Cardiovascular Disease

DIAGNOSIS AND TREATMENT OF

Cardiovascular Disease

Edited by

WILLIAM D. STROUD, M.D., F.A.C.P.
Late Professor of Cardiology,
University of Pennsylvania Graduate School of Medicine

and

MORRIS W. STROUD, 3rd, M.D.
Associate Professor of Medicine, Western Reserve University

CONTRIBUTORS

EDGAR V ALLEN, M D
RACHEL ASH, M D
HUGH BARBER, M D
NELSON W. BARKER, M D
DAVID P BARR, M D
CLAUDE S BECK, M D.
SAMUEL BELLET, M D
MARION A. BLANKENHORN, M D.
JULIO C. DAVILA, M D
ARTHUR C DEGRAFF, M D
WILLIAM DOCK, M D
THOMAS M DURANT, M D
J. EARLE ESTES, M D.
MORTIMER S FALK, M D
NORMAN E FREEMAN, M.D
ROBERT P. GLOVER, M D.
FRANCIS C GRANT, M D
RICHARD S GUBNER, M D.
BURTON E HAMILTON, M D
JOSEPH M. HAYMAN, JR , M D
GEORGE R. HERRMANN, M.D
EDGAR A. HINES, M D
ORVILLE HORWITZ, M D
JOSEPH HUGHES, M.D.
FRANKLIN D JOHNSTON, M D
JOHN T KING, JR , M D
JOSEPH D B KING, M.D
SAMUEL A LEVINE, M D
JERROLD S. LIEBERMAN, M D
ALEXANDER MARGOLIES, M D
CURRIER MCEWEN, M D
THOMAS M. MCMILLAN, M D
HERMAN O MCPHEETERS, M D
WILLIAM R. MINNICH, M D
A M OSHLAG, M D
IRVINE H. PAGE, M D
JOHN R PAUL, M.D
JAMES E PAULLIN, M D
L LEWIS PENNOCK, M D
RENO R PORTER, M D
WILLIAM B PORTER, M D
ERNEST W REYNOLDS, JR , M D
HUGO ROESLER, M D.
HOWARD A RUSK, M D
TRUMAN G SCHNABEL, JR , M D.
HOWARD B. SPRAGUE, M D
ISAAC STARR, M D
EDWARD J STIEGLITZ, M D
JOHN H STOKES, M D
JOHN E STRANG, M D
MORRIS W STROUD, 3RD, M D.
WILLIAM D STROUD, M D
HENRY M. THOMAS, JR , M D.
HARRY E UNGERLEIDER, M D.
JOSEPH A WAGNER, M D
EDWARD WEISS, M D
PAUL D. WHITE, M D.
FREDRICK A WILLIUS, M D
WILLIAM L WINTERS, JR , M D.
CHARLES C WOLFERTH, M D
IRVING S. WRIGHT, M D.
JACOB ZATUCHNI, M D

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GEORGE W NORRIS, M D


SIR THOMAS LEWIS

THIS BOOK

IS GRATEFULLY DEDICATED

BY ITS EDITORS

TO

GEORGE W. NORRIS, M. D.

AND

THE LATE SIR THOMAS LEWIS

WITH DEEP APPRECIATION OF THEIR FRIENDSHIP,

INSTRUCTION, AND WISE COUNSEL

Contributors

EDGAR V. ALLEN, M.D., F.A.C.P
Senior Consultant in Medicine, Mayo Clinic, Professor of Medicine, University of Minnesota (Mayo Foundation for Medical Education and Research)
ROCHESTER, MINN.

RACHEL ASH, M D.
PHILADELPHIA, PA.

HUGH BARBER, M D , F R C.P
Consulting Physician to Derbyshire Royal Infirmary
DERBYSHIRE, ENGLAND

NELSON W BARKER, M D , M S. (MED), F.A C.P.
Consultant in Medicine, Mayo Clinic; Professor of Medicine, University of Minnesota Graduate School (Mayo Foundation)
ROCHESTER, MINN

DAVID P. BARR, M.D., F A C P
NEW YORK, N Y.

CLAUDE S. BECK, M D
Professor of Cardiovascular Surgery, Western Reserve University School of Medicine and University Hospitals
CLEVELAND, OHIO

SAMUEL BELLET, M D , F A C P.
Professor of Clinical Cardiology, University of Pennsylvania Graduate School of Medicine; Director, Division of Cardiovascular Disease, Philadelphia General Hospital
PHILADELPHIA, PA.

M A. BLANKENHORN, M D.
Professor Emeritus, Department of Medicine, University of Cincinnati College of Medicine, Director of Medicine, Jewish Hospital Association, Cincinnati, Ohio

JULIO C DAVILA, M.D
PHILADELPHIA, PA.

ARTHUR C DEGRAFF, M D , F.A C.P
Professor of Therapeutics, New York University College of Medicine, New
NEW YORK, N. Y.

WILLIAM DOCK, M D , F.A C.P.
Professor of Medicine, State University of New York Downstate Medical Center; Visiting Physician, Kings County Hospital
BROOKLYN, N Y.

THOMAS M. DURANT, M.D , F A C P
Professor of Medicine and Chairman of
Board of Internal Medicine
PHILADELPHIA, PA.

J EARLE ESTES, M D, M S (MED), F.A C P.
Assistant Professor of Medicine, University of Minnesota, Graduate School (Mayo Foundation)
ROCHESTER, MINN

MORTIMER S FALK, M D , M S P.H.
Instructor, Department of Dermatology and Syphilology, University of Pennsylvania School of Medicine
PHILADELPHIA, PA.

NORMAN E. FREEMAN, M D.
Associate Clinical Professor of Surgery, University of California Medical School

ROBERT P. GLOVER, M.D.
Assistant Professor Clinical Surgery, University of Pennsylvania School of Medicine; Director of Thoracic and Cardiovascular Research Laboratory, [illegible]
PHILADELPHIA, PA.

FRANCIS C. GRANT, M D
Professor of Neurological Surgery, University of Pennsylvania School of Medicine
PHILADELPHIA, PA

RICHARD S. GUBNER, M.D , F.A C P
Assistant Professor of Clinical Medicine, Long Island College of Medicine, Assistant Medical Director, Equitable Life Assurance Society of the United States
NEW YORK, N. Y.

BURTON E HAMILTON, M.D , F.A C.P.
Consultant Cardiologist at the Boston Lying-in Hospital; Cardiologist New England Deaconess Hospital
BOSTON, MASS

JOSEPH M HAYMAN, JR , M.D , F A C P
Dean and Professor of Medicine, Tufts University School of Medicine, Senior Physician, New England Center Hospital
BOSTON, MASS

GEORGE R HERRMANN, M D , PH. D
Professor of Medicine and Director of the [illegible] *Base Hospital, and Galveston Marine Hospital*
GALVESTON, TEXAS

EDGAR A HINES, JR , M D , M S (MED), F A C P.
Consultant Section of Medicine Mayo Clinic; Professor of Medicine, University of Minnesota, Graduate School, Mayo Foundation
ROCHESTER, MINN

ORVILLE HORWITZ, M.D
Assistant Professor of Clinical Medi- [illegible] *Mawr Hospital*
PHILADELPHIA, PA

JOSEPH HUGHES, M D.
[illegible]
PHILADELPHIA, PA

FRANKLIN D JOHNSTON, M.D.
Professor of Internal Medicine, University of Michigan Medical School
ANN ARBOR, MICH

JOHN T KING, JR , M.D , F.A C P.
Associate Professor of Medicine Emeritus, Johns Hopkins University School of Medicine
BALTIMORE, MD

JOSEPH D. B KING, M.D
Instructor in Medicine, Johns Hopkins University School of Medicine, and University of Maryland Medical School; Physician, Johns Hopkins Hospital and Baltimore City Hospitals
BALTIMORE, MD

SAMUEL A. LEVINE, M.D., F A C P
Clinical Professor of Medicine, Harvard Medical School; Physician, Peter Bent Brigham Hospital
BOSTON, MASS

JERROLD S LIEBERMAN, M.D.
[illegible]
NEW YORK, N Y

ALEXANDER MARGOLIES, M.D , F A C P.
Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine
PHILADELPHIA, PA

CURRIER MCEWEN, M.D , F A C.P.
Professor of Medicine and Chairman, Rheumatic Diseases Study Group, New York University College of Medicine; Visiting Physician, Bellevue Hospital and University Hospital; Consultant, Goldwater Memorial Hospital and Manhattan Veterans Administration Hospital
NEW YORK, N Y

THOMAS M MCMILLAN, M D., F.A C.P.
Professor of Clinical Medicine, University of Pennsylvania School of Medicine; Professor of Clinical Cardiology, [illegible]
PHILADELPHIA, PA

HERMAN O. MCPHEETERS, M D.
Member of the Staff of Asbury Methodist, Mount Sinai, and Northwestern Hospitals
MINNEAPOLIS, MINN

WILLIAM R. MINNICH, M.D, F.A C P.
Teaching Fellow, Emory University Medical School Member of Teaching Staff, Piedmont Hospital
ATLANTA, GA.

A. M. OSHLAG, M D.
Emory University Medical, Grady Memorial Hospital
GRIFFIN, GA.

IRVINE H PAGE, M D, F A C P
Director of Research, Division of Research, Cleveland Clinic Foundation; Professor of Experimental Medicine, The Frank E Bunts Educational Institute; Past President, American Heart Association
CLEVELAND, OHIO

JOHN R. PAUL, M D., F A C.P.
[illegible]
NEW HAVEN, CONN

JAMES E PAULLIN, M D, M A C P
Professor of Clinical Medicine, Emory University School of Medicine
ATLANTA, GA.

L. LEWIS PENNOCK, M.D.
Assistant Professor of Medicine, School of Medicine, University of Pittsburgh
PITTSBURGH, PA.

RENO R PORTER, M.D
Associate Professor of Medicine and Director of Cardiovascular Teaching Program, Medical College of Virginia
RICHMOND, VA

WILLIAM B PORTER, M D, F A.C.P.
[illegible]
RICHMOND, VA

ERNEST W. REYNOLDS, JR, M D
Associate Professor of Medicine, University of Michigan Medical School
ANN ARBOR, MICH

HUGO ROESLER, M D., F.A C.P.
Associate Professor of Medicine (Cardiology) Temple University School of Medicine
PHILADELPHIA, PA

HOWARD A. RUSK, M D, F A C P
Professor and Chairman, Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center
NEW YORK, N. Y

TRUMAN G. SCHNABEL, JR, M D
Associate Professor of Medicine, Uni- [illegible] *of Pennsylvania*
PHILADELPHIA, PA

HOWARD B. SPRAGUE, M D, F.A C P.
Lecturer on Medicine, Harvard Medical School, Member of Board of Consultation, Massachusetts General Hospital
BOSTON, MASS

ISAAC STARR, M D
Hartzell Research Professor of Therapeutics, University of Pennsylvania
PHILADELPHIA, PA

EDWARD J. STIEGLITZ, M D, M S, F A C P
[illegible] *Hospital*
WASHINGTON, D C.

JOHN H STOKES, M D.
[illegible]
PHILADELPHIA, PA

JOHN E. STRANG, M D
[illegible] *Hospital*
PHILADELPHIA, PA

MORRIS W. STROUD, 3RD, M D
Associate Professor of Medicine, Western Reserve University; Associate Physician, University Hospitals; Associate [illegible]
CLEVELAND, OHIO

WILLIAM D. STROUD, M D , F.A C P
Professor of Cardiology, University of [illegible]
Heart Hospitals
PHILADELPHIA, PA

HENRY M. THOMAS, JR , M D , F A C P
Associate Professor of Medicine, Johns Hopkins University School of Medicine, Attending Physician, Johns Hopkins Hospital
BALTIMORE, MD

HARRY E UNGERLEIDER, M D
Director of Medical Research, Equitable Life Assurance Society of the United States
NEW YORK, N Y

JOSEPH A WAGNER, M D
Assistant Professor of Clinical Medi- [illegible]
General U S Army
BRYN MAWR, PA

EDWARD WEISS, M.D., F A C.P.
Professor of Clinical Medicine, Temple University School of Medicine
PHILADELPHIA, PA

PAUL D. WHITE, M.D., F.A C.P.
Executive Director, National Advisory Heart Council; Consultant in Medicine, Massachusetts General Hospital
BOSTON, MASS

FREDRICK A. WILLIUS, M.D , M.S (MED), F A.C P
Emeritus Professor of Medicine, Mayo [illegible]
versity of Minnesota
ROCHESTER, MINN

WILLIAM L WINTERS, JR., M D
Instructor in Internal Medicine and Member of Department of Cardiology, Temple University Medical School
PHILADELPHIA, PA

CHARLES C WOLFERTH, M D., F A.C.P
Professor of Medicine, University of Pennsylvania School of Medicine
PHILADELPHIA, PA

IRVING S WRIGHT, M D., F A C P.
Professor of Clinical Medicine, Cornell [illegible]
General, U S Army
NEW YORK, N Y

JACOB ZATUCHNI, M D
Assistant Professor of Internal Medicine, Temple University Medical School and Hospital
PHILADELPHIA, PA

Foreword to 1959 Revision

The loose-leaf binding of Diagnosis and Treatment of Cardiovascular Disease began in 1957 with the Fifth Edition. Revisions and additions were promised as deemed necessary to keep the chapters up to date. In fulfillment of this promise, nine chapters have been revised and three chapters added.

Among the chapter revisions, Arterial Hypertension by Dr. Irvine H. Page, Rheumatic Heart Disease by Dr. Currier McEwen, Rehabilitation of the Patient with Cardiovascular Disease by Dr. Howard Rusk, and Congenital Cardiovascular Abnormalities by Dr. Rachel Ash embrace recent concepts and findings in areas where rapid progress is being made.

The other revised chapters include The Heart in Diseases of the Endocrine Glands by Dr. David P. Barr, Coronary Disease Including Angina Pectoris by Drs. W. D. Stroud and M. W. Stroud, The Heart in Pulmonary Disease by Drs. William L. Winters, Jr., and Thomas M. Durant, Disturbances of the Heart Beat by Dr. George R. Herrmann, and Bacterial Endocarditis by Dr. William Dock.

The Historical Origin and Evolution of Certain Congenital Anomalies of the Heart and Great Vessels, a new chapter, by Dr. Fredrick A. Willius, records the historical aspects of the surgical treatment of certain of the congenital anomalies of the heart and great vessels.

Drs. Jerrold S. Lieberman and Irving S. Wright have contributed a new chapter, Use of Anticoagulants in Treatment of Thromboembolic Disease, which deals with the indications and contraindications for anticoagulant therapy in such conditions as thrombophlebitis, acute myocardial infarction, and rheumatic heart disease, as well as in the fields of dentistry, ophthalmology, obstetrics and gynecology.

The new chapter, Cardiac Catheterization, by Dr. Truman G. Schnabel, Jr., is especially recommended for its clear and concise description of diagnostic findings in certain cardiac abnormalities by a relatively new technique.

Unfortunately, Dr. William D. Stroud, the original editor and uncle of the junior editor, died August 19, 1959, from lung cancer. His untimely death is mourned by his family, fellow physicians, and the thousands of grateful patients who benefited not only from his diagnostic and therapeutic skills but also from his almost unique ability to restore optimism and confidence.

To aid in further revisions, additions and deletions as deemed necessary the publishers and junior editor are seeking a qualified co-editor.

Thanks are extended to the authors of the new chapters and to the former authors for work in the revision of their contributions. Gratitude is also due to members of the staff of the F. A. Davis Company for their help in preparing and indexing both new and revised chapters.

MORRIS W. STROUD, 3RD, M.D.

Foreword

Within living memory, our knowledge both of maladies of the heart and, more recently, of diseases of the peripheral circulation, has profoundly changed; it has become far more exact and far more comprehensive than formerly; it continues to grow rapidly. These changes have been brought about chiefly in the English-speaking countries, and not least in the United States of America. The brilliant list of American authors of the present contents includes a score of names known in every part of the world where cardiovascular diseases have been intensively studied; they are known for the solid contribution of those who bear them to their subject. Rarely before has such a number of authoritative writers combined to place its views of a branch of medicine on record, and never before of cardiovascular disease; it is a guarantee to the reader that he is in direct or close contact with all the fountains of modern knowledge, the most important guarantee perhaps that any reader can be given

Preface to the Fifth Edition

Although many, many books written on heart disease are continuously coming off the presses yet it seems to our Publishers and to your Editors that bringing these volumes up to date in loose leaf form is a worthwhile project.

The problem of cardiovascular disease has become so large and so complicated that it appears to us impossible for one man to write a completely satisfactory book on this subject. We have been unusually fortunate in the cooperation of the outstanding authorities in cardiovascular disease in this country, and whatever value these volumes have is almost entirely due to them.

Since there are in all fifty-nine contributors, and since the various problems of cardiovascular disease are so closely related, there has been necessarily some overlapping. In our opinion, this is justifiable, since it is seldom that two authorities have exactly the same ideas concerning any cardiovascular problem.

Although these volumes cover the entire subject of cardiovascular disease, the form is not encyclopedic. There is no chapter on the prognosis in different types of cardiovascular disease, since this subject is considered in the various chapters.

There has been a radical revision of these volumes in this edition. Practically every chapter has been revised and brought up to date with additional references.

With loose leaf binding it will be possible to keep the chapters up to date and to continuously revise them in the light of newer concepts and advancements in the various aspects of cardiology. Revisions and additions will be issued as the Editors deem necessary.

A criticism of the past editions has been that they did not cover the subject completely and hence could not be used as reference volumes This, of course, depends upon the index as much as the contents. We believe this criticism has been overcome through the new and complete index which has been prepared by one who is well trained and experienced in such matters.

Although we hesitate to draw attention to any of the chapters specifically, yet some of the chapters should be mentioned·

The section on surgery has been covered in an outstanding manner by Dr. Claude S. Beck in "Surgery of the Heart and Pericardium," and Dr Robert R. Glover and Dr. Julio C. Davila in "Surgery of the Cardiovascular System." As in the Fourth Edition attention should be drawn to the chapter on "Electrocardiography," by Dr. Samuel Bellet and Dr. Thomas M McMillan. Any physician can find an almost exact duplicate for most electrocardiograms among the figures in this chapter, and from

the text make a conservative and accurate interpretation of such electrocardiograms; although, in our opinion, it is important for any physician using a galvanometer to take a course in electrocardiography before attempting to interpret electrocardiograms.

There has been a determined effort to secure many illustrative case histories, since this is recognized as a practical method of presenting the necessary procedures for diagnosis and effective treatment.

Although it is impossible to include pictures of all the men who have contributed toward the advancement of the knowledge of cardiovascular disease yet some have been chosen by Dr. William G. Leaman as the most outstanding.

The arrangement of the material in the previous editions has been criticized. This arrangement was based upon the Nomenclature and Criteria for Diagnosis of Diseases of the Heart as published by the American Heart Association; namely, etiological, anatomical, physiological, and treatment with peripheral vascular disease at the end In this edition, as far as possible, treatment follows the various etiological types of cardiovascular diseases.

Nothing that we may say can adequately express our gratitude to those who have contributed to these volumes, and we heartily agree with the late Sir Thomas Lewis in his remarks concerning their qualifications as authorities upon the subjects which they have discussed.

Again we wish to thank the F. A Davis Company and particularly Frederick C. Smith, M D. and Mrs Florence W. Brehm for their kindness and helpfulness in preparing these volumes.

William D. Stroud, M.D.
Morris W Stroud, III, M.D.

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Cardiovascular Disease

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I

Historical Comments Pertaining to Cardiology

It is impossible to appreciate and understand fully the remarkable achievements of modern medicine without a general knowledge, at least, of the historical events which made possible the exalted position of modern medicine. Furthermore, the future of medicine cannot be plotted wisely if the errors of the past and the present remain unrecognized and are therefore perpetuated.

Medicine and astronomy were the first of the natural sciences, and the long and noble tradition of medicine is inseparably linked with the evolutionary ascendancy of civilization and the welfare of mankind. The history of medicine, like history in general, represents great cycles of events and human activity. The span of these cycles is not precise but extends from one era to another and often bridges several eras. One cycle may not yet be complete when another cycle has its inception. History is actually the record of the actions of man, based on thought, understanding, initiative and accomplishment. It is profoundly influenced by customs, contemporary events, opportunities and adversities, religious beliefs and various prohibitions, economic and political conditions, wars, famines, and epidemics.

Therefore, to appreciate fully the history of medicine it is necessary to appraise the overall cyclic pattern and to regard the individuals, who for good or for bad, have enacted their roles in the evolution of the magnificent yet uncompleted pageant which we know as "modern medicine."

It would be impossible to record comprehensively the historical development of knowledge relating to the heart and circulation within the limitations of a chapter. Therefore, emphasis will be accorded the historical milestones pertaining to the evolution of physical diagnosis with special reference to the heart.

Modern medicine finds itself in an era of mechanization. Almost countless new methods of diagnosis have been introduced, and while each method is of limited importance, through wise utilization and judicious interpretation each becomes a valuable adjunct to diagnostic procedures. In modern medical philosophy, a tendency exists to subordinate the importance of physical diagnosis. This is true not only in practice, but also, unfortunately, in teaching. The time has not come when diagnostic ad-

juncts can or should supersede the basic and time-tested methods of physical diagnosis.

The utilization of inspection and palpation is clearly described in the earliest medical records, the Egyptian papyri These documents, inscribed on a paper-like material, derived their name from the fact that the fabric was prepared from the fibers of the reed, Cyperus papyrus, which grew in profusion along the banks of the river Nile. Seven of them deal with medical and surgical subjects.

The Edwin Smith Surgical Papyrus, the last to be discovered but the oldest in space of time, was discovered in Thebes in 1862. It was found by Edwin Smith, the first American Egyptologist. This valuable document came into possession of Smith's daughter after his death and she in turn presented it to the New York Historical Society in 1906; it remained in obscurity until 1920. The society then invited J. H. Breasted, of the Oriental Institute of the University of Chicago, to decipher and translate the manuscript. Breasted published his results in 1930.

Breasted dated the Edwin Smith Surgical Papyrus from the seventeenth century B. C. but insisted that the author's original manuscript was inscribed at least one thousand years earlier during the Pyramid Age (3000-2500 B. C). He believed that the author may have been Imhotep, the first known physician and architect.

These early documents indicated that fractures, superficial tumors, large deep-seated tumors, and the enlarging gravid uterus were observed and palpated. The Edwin Smith Surgical Papyrus also contains a record of the earliest attempt to palpate and count the peripheral arterial pulse. This was undoubtedly done by means of the water clock which was a product of ancient Egyptian ingenuity.

The preservation of the papyri was not a matter of chance but clearly rested in the religious beliefs of the Egyptians. These people of antiquity held the belief that the soul of the departed continued to live and that it passed before their supreme diety, Osiris, in judgment of earthly deeds or misdeeds. The soul then returned to the body to dwell there throughout eternity. Thus, provisions were made to permit the body also to exist eternally.

This religious belief was the basis for the Egyptians' ingenious method of mummification, the success of which was favored by a relatively arid climate. The mummified body was placed in a sarcophagus with the intent of further preservation and the tombs varied from small and unpretentious structures of stone to the mighty pyramids. Objects were placed within the structures for the comfort of the returned soul, such as food and drink, jewels, various papyri, vessels of many types, and chariots in the case of the Pharaohs. Thus, the valuable documents of antiquity could not have survived the ravages of time and weather but for the ingenious actions of man based on religious beliefs.

Similar data pertaining to inspection and palpation also have been derived from the ancient civilizations of China and India.

Important advances in physical diagnosis did not occur until the Golden Age of early Greek civilization which, from a medical standpoint,

had its inception in the life of Hippocrates (493-429 B. C.) of Cos. Hippocrates has probably been the most controversial personality in all medical history; virtually every statement regarding his life and works has been questioned if not contradicted. Jones referred to "the shadowy Hippocrates of ancient tradition," while Sigerist stated "all that we certainly know of Hippocrates is that he lived."

The famous Hippocratic Works were probably written by contemporaries and successors of Hippocrates, as evidenced by the fact that they contain many contradictions. It is probable that the Aphorisms were Hippocrates' own products. He formulated the doctrine which appears to be the true beginning of physical diagnosis wherein he advocated and practiced the utilization of mental concentration and analysis together with the application of the five senses in the diagnosis of disease.

Gee stated that the ancient Greeks used the method of tapping to differentiate ascites from tympanites, but this was not the true beginning of percussion.

During the ensuing centuries little progress was made in physical diagnosis, in a large measure owing to the fact that the complex anatomic maze of the human body was slowly and often erroneously revealed.

Finally an illustrious personality appeared in the medical world who conceived an erroneous idea concerning the structure of the heart and the vascular system and their functions. Either Claudius Galen (138-201 A.D.) of Pergamon, Asia Minor, and subsequently of Rome, was a man of great persuasive powers or his contemporaries and many generations of his successors were gullible and without critical insight, for his errors were accepted and perpetuated for nearly fourteen and a half centuries. As late as 1649, Jean Riolan (Riolanus) (1577-1657) of Paris, a fanatical admirer of Galen's teachings, remarked that if subsequent observations and dissections differed from those of the great master (Galen), any variations were attributable to the fact that nature had changed.

Galen's anatomic observations were incorrect and he amplified these errors by concocting speculative physiologic fallacies to condone his anatomic mistakes. He possessed no idea whatsoever of the basic physiologic principle of the circulation of the blood.

In this period of history most dissections were performed on animals and occasionally on stillborn infants. It was not until the close of the fifteenth century that dissection of cadavers was officially authorized when a bull to this effect was issued by Pope Sixtus IV.

In the succeeding centuries considerable progress in the medical sciences became evident. Notable progress occurred in embryology; significant strides were made in pathologic anatomy, and histology became an established science through the efforts and contributions of such celebrities as van Leeuwenhoek, Malpighi, and Spallanzani.

Only two outstanding medical events occurred during the Medieval Era (1096-1453). The first was the correct description of the pulmonary circulation by the great Arabian physician, Ibn an-Nafis (circa 1210-1288), of Cairo. Credit for the first description of the pulmonary circulation has usually been accorded the martyr, Michael Servetus (1509-1553), of Villa-

nueva de Sigena, Spain, who independently and without knowledge of his predecessors' contribution recorded his own findings in 1553. The work of Ibn an-Nafis was not generally known until the investigations of Meyerhof and of Haddad and Khairallah were published in 1935 and 1936. Ibn an-Nafis' description of the pulmonary circulation was found in his Commentary on Avicenna's Anatomy.

The second great medical event in this era which influenced the field of cardiac diagnosis at least indirectly was the founding of the famous school of Salerno, during the reign of Frederick II (1215-1250). This great school was based on the modern concept of organization, as an attempt was made to secure teachers who were the most talented and whose viewpoints varied. Teachers were sought from afar, and the faculty was created without national or racial prejudice. It comprised Greeks, Italians, Persians, Jews, and the monks of Western Europe.

The Renaissance (1453-1600) or the era which witnessed the awakening of culture, science, and the arts brought forth distinguished contributors to the medical sciences This was particularly true in the field of anatomy where such celebrated men as da Carpi (1470-1550), Vesalius (1514-1564), Canano (1515-1579), Guido Guidi (Vidius) (?-1569), and many others contributed generously to the understanding of many of the structural complexities of the human body. While no new innovations concerned with the diagnosis of diseases occurred, the increased understanding of anatomy was clearly a preface which made subsequent contributions possible.

Probably the most gifted and diversely talented contributor of the Renaissance was the fabulous Leonardo da Vinci (1452-1519). Commonly known as an artist of rare ability he was likewise an anatomist of distinction. His drawings revealed the general character of the heart, the main coronary vessels, and their large tributaries, and in at least one of the drawings he attempted to schematize the "invisible pores" of Galen in the interventricular septum. Leonardo discovered and described the moderator band of the right ventricle. In addition to the aforementioned accomplishments, he was the pioneer of exquisite medical illustration, an inventor, architect, engineer, expert ballistician, geologist, geographer, and astronomer.

Nearly a century and a quarter elapsed after the Renaissance before the forthcoming of a significant contribution to physical diagnosis. A resourceful Italian physician, Francesco Ippolito Albertini (1662-1738) of Bologna introduced a method for determining enlargement of the heart. He was a pupil of the famous Malpighi and a friend and contemporary of Valsalva. Albertini was particularly interested in the correlation of signs of disease and postmortem findings. He carefully studied the apex beat of the heart by means of inspection and palpation and utilized the character of the apex beat and its outward displacement as signs of enlargement of the organ. Albertini's observations appeared in 1726 in his work, "De affectionibus cordis."

The next important component in physical diagnosis was brought forth 35 years later when Joseph Leopold Auenbrugger (1722-1809) introduced

percussion. He was born in Graz, Styria in Austria and was the son of an innkeeper. The fact that Auenbrugger was the son of an innkeeper has singular significance in the story of his discovery.

During his youth he was obliged to help his father in the duties of the inn. In those days the process of tapping was used to determine whether walls were solid or contained hollow hiding places, and innkeepers utilized the method to determine the level of the fluids in kegs. Young Auenbrugger undoubtedly became expert in this procedure. Another significant fact relating to his discovery was his musical talent and early training in music.

Auenbrugger studied medicine at Vienna under van Swieten, founder of the old Viennese school of medicine and originator of its famous library. Van Swieten in turn had been a student of the famous Boerhaave. From 1751 to 1762 Auenbrugger was associated with the Spanish Hospital in Vienna, first as assistant and later as physician. It was during this tenure that he made his classic observations after seven years of diligent and painstaking work.

After describing the sounds produced by tapping various regions of the healthy thorax and the technic of percussion, Auenbrugger described the changes produced by disease as revealed by postmortem examination. His work was published in 1761 under the title, "*Inventum novum ex percussione thoracis humani ut signo abstrusos interni pectoris morbos detegendi.*"

Auenbrugger came near to discovering auscultation, as revealed by the Eleventh Observation in his "*Inventum novum.*" A brief excerpt from the translation follows: "If at this time, while the patient is coughing and spitting, the palm of the hand be placed over the site of the vomica, that is, over the place where its existence had been detected by percussion, the noise of the fluid within the chest will be sufficiently manifest."

Auenbrugger's discovery was generally ignored and even his teacher, van Swieten, did not accept the new method of diagnosis. Only two European physicians, Stoll of Vienna and Charles G. Ludwig of Leipzig, acclaimed and practiced the method. The "*Inventum novum*" was translated into French by Rozierre in 1770 and twice into English but continued to be quite universally ignored for nearly fifty years, when the great French clinician, Jean-Nicolas Corvisart (1755-1821) of Paris, acclaimed and practiced percussion. Corvisart, who was Laënnec's teacher and personal physician to Napoleon Bonaparte, had worked with percussion for many years after studying Auenbrugger's book. Corvisart made his own translation of this work, giving Auenbrugger full credit for the discovery, and added his own experience with percussion in the diagnosis or disease. Corvisart's book was published in 1808, and from then on percussion became universally accepted as the third component of physical diagnosis.

Before the age of sixty, Auenbrugger had written a libretto for the celebrated Italian composer, Antonio Salieri The opera, "Der Rauchfangkehrer" (The Chimney Sweep) was presented in Vienna in 1781 and attracted favorable comment from Empress Maria Theresa who urged

Auenbrugger to continue with his musical works. However, he demurred stating that his first responsibility was to further the science of medicine.

In 1784 Emperor Joseph enobled Auenbrugger, not for his great medical discovery, but for his untiring services to the poor. Auenbrugger became wealthy but continued unselfishly to give of his time to the many indigent persons who sought his services.

Auenbrugger and his wife celebrated their golden wedding anniversary in 1804 and soon thereafter his wife died. He never recovered from his grief which, combined with the failing health of age, eventuated in the development of an acute respiratory infection that caused his death five years later at the age of eighty-seven years.

In 1828, Pierre-Adolphe Piorry (1794-1879) of Poitiers invented the pleximeter and hoped to improve on Auenbrugger's method of percussion. His work appeared in Paris under the caption, "*De la percussion médiate.*" Piorry's method was never universally adopted although the pleximeter was used by some clinicians even in the early part of the present century.

The completion of the tetralogy of physical diagnosis occurred in 1819, when René-Théophile-Hyacinthe Laennec (1781-1826) discovered auscultation and published his classic work on the subject. He was born in Quimper in lower Brittany, the first child of a tuberculous mother. There were a younger brother, Michel, and two younger sisters. The mother died soon after the birth of the second daughter. The father, an unsuccessful lawyer, was unable to care for the children so arrangements were made for a paternal uncle to bring up the two boys.

The uncle, Guillaume François Laennec, was a famous physician. He was a student of the celebrated John Hunter and became Professor of Medicine at Nantes. It is probable that the uncle's influence played an important part in René's determination to study medicine.

René was a frail and impressionable child and, unfortunately, witnessed many of the horrors of the French Revolution. A guillotine was within sight of the boy's home. The revolution had a profound effect on French medicine, as evidenced by the fact that from 1786 to 1789 not one medical student was graduated by the Paris Faculty.

Toward the close of this tragic period of France's history, young Laënnec began the study of medicine in 1795. He first studied medicine at L'Hotel Dieu in Nantes and five years later entered L'Ecole de Medecine in Paris. Laennec studied medicine under the great Corvisart, physiology under the guidance of Bichat, and surgery under the famous Dupuytren.

Laënnec's first published work while still a medical student was concerned with mitral stenosis found at necropsy. Shortly before his graduation in 1804, he proved that phthisis and pulmonary tuberculosis were one and the same disease.

For five years after his graduation, Laénnec lectured on pathologic anatomy and engaged in private practice. In 1812 he was appointed physician to Beaujon Hospital and four years later was named to the staff of Necker Hospital where he made his famous discovery. In 1819 Laënnec's classic work, "Traité de l'auscultation médiate," was published. It is of interest

to note the ensuing portion of the introduction to his book as it appears in the first American edition published in 1823.

"In 1816, I was consulted by a young woman laboring under general symptoms of diseased heart and in whose case percussion and the application of the hand were of little avail on account of the great degree of fatness. The other method just mentioned being rendered inadmissible by the age and sex of the patient, I happened to recollect a simple and well-known fact in acoustics, and fancied at the same time, that it might be turned to some use on the present occasion. The fact I allude to is the augmented impression of sound when conveyed through certain solid bodies, as when we hear the scratch of a pin at one end of a piece of wood, *applying our ear to the other. Immediately, on this suggestion, I rolled* a quire of paper into a sort of cylinder and applied one end of it to the region of the heart and the other to my ear, and was not a little surprised and pleased, to find that I could thereby perceive the action of the heart in a manner much more clear and distinct than I had ever been able to do by the immediate application of the ear. From this moment I imagined that the circumstances might furnish means of enabling us to ascertain the character, not only of the action of the heart, but of every species of sound produced by motion of all the thoracic viscera."

Laënnec's book warrants study even today. Its comprehensiveness in some respects is similar to a modern text. Laennec described and discussed pulsations of the heart, heart sounds, rhythm, irregularities, and the symptoms of heart disease. He believed the anginal syndrome to be a nervous affection. The volume includes discussions of cardiac hypertrophy and dilatation, fibrosis, atrophy, fatty degeneration, calcification, carditis, endocarditis, pericarditis, tubercles, cardiac thrombosis, malformations, displacements, aneurysm, and congestion of the viscera in heart failure.

Laennec recognized the fact that the first heart sound is associated with systole of the ventricle, but erroneously believed that the second sound was due to systole of the auricle. He also described thrills and venous hums and commented on their origin and significance.

Laënnec's work was not accepted at first in his native country but was eagerly acclaimed by physicians of neighboring countries, especially by those of the British Isles who attended his clinic in large numbers. With the acceptance of auscultation by the physicians of England, Scotland, and Ireland, these schools of medicine forged rapidly ahead and produced such outstanding celebrities as Stokes, Graves, Adams, Cheyne, Corrigan, Parry, and Jenner.

Laennec was always a frail person and suffered for many years from a *chronic asthmatic bronchitis. In 1828 he became seriously ill from an* acute respiratory illness and died at the premature age of 45 years. Few physicians at that age have contributed so greatly to medicine and received such broad recognition as did René-Théophile-Hyacinthe Laennec.

The physician who advanced physical diagnosis to its acme of science *and art was Josef Skoda (1805-1881) of Vienna. He was born in Pilsen,* Bohemia, the son of a locksmith. It is interesting to note that his father's modest little shop finally developed into the large Skoda works, which to

a large extent furnished arms and munitions to Germany during World War I.

Young Skoda was graduated from the University of Vienna in 1831, and taught physics and mathematics to aid in his own support while securing his education. He was an apt and diligent student, was painstakingly thorough, and possessed the gift of concentration on important details. Skoda secured a subordinate position at the Allgemeines Krankenhaus in Vienna after his graduation and worked under the guidance of Rokitansky, Draut, and Wirer.

Skoda early in his medical career became greatly interested in percussion and auscultation and spent many hours at the bedside interrogating and examining patients. He was meticulously thorough in his examinations and was possessed of almost inexhaustible patience. However, his progress was slow because he was eclipsed by numerous internationally known satellites.

Skoda's great moment of opportunity came while he was still a young man. The French minister to Austria, the Duc de Blacas, became seriously ill and such celebrities as Malfatti, Turckheim, and Wirer had identified the illness as due to disease of the liver. For some reason young Skoda was requested to examine the Duc. After a deliberate and thorough examination, Skoda refuted the previous diagnosis and submitted his own diagnosis of aneurysm of the abdominal aorta. Shortly thereafter the Duc died and postmortem examination confirmed Skoda's diagnosis.

This feat on the part of an earnest, young but obscure physician impressed the great Turckheim, who immediately took a great interest in Skoda and created teaching opportunities for him. For many years Skoda was professor of medicine at the Allgemeines Krankenhaus in Vienna where clinical material was abundant and postmortem examinations were plentiful. In this environment of medical opportunity, Skoda elevated physical diagnosis to its greatest heights. His classic work, *"Abhandlung über Perkussion und Auskultation,"* appeared in 1839.

Skoda's clinic was one of the most popular of the day and attracted students from all over the world. One of the last American students to attend Skoda's clinic was the late Charles H. Hoover who lost his life in the Cleveland Clinic tragedy of 1927.

Many others, of course, have participated in the development of physical diagnosis—they are too numerous to mention here. In the light of the accomplishments of all these illustrious predecessors, it is discouraging to find the science and the art of physical diagnosis threatened into subservience by an almost inexhaustible array of mechanistic diagnostic adjuncts.

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HOWARD B. SPRAGUE, M.D.
AND
PAUL D. WHITE, M.D.

2

Introduction to Diseases of the Cardiovascular System*

Introduction: One of the most useful contributions to progress in the study of disease is a proper definition of terms and a classification of diagnoses based upon a complete analysis of the various syndromes. In cardiovascular disease this has proved most practical by describing the diagnosis of each case from the standpoint of the etiological factor responsible for the *disease, the changes in the structure of the tissues or organs involved,* the disturbances of their function, and the interference by the disease with bodily activity. By including in this way a fourfold explanation of the status of the heart or blood vessels, we avoid vague categories of the past which have described only one aspect of the disease such as "mitral regurgitation," "auricular fibrillation," "dropsy," or "intermittency of the pulse." Therefore, for satisfactory diagnosis of the condition of a patient suffering from heart disease at least one subheading from each of the four main divisions of the following classification must usually be included. This classification modifies somewhat those previously published but corresponds in the main to the latest outline prepared for the American Heart Association.**

ETIOLOGICAL

Congenital Cardiovascular Defect: This is an unexplained aberration of *development, thought to be due generally to faulty germ plasm and rarely* to intrauterine infection.

Recent studies have shown an apparent relationship between the combination of congenital cataract and certain congenital heart lesions, and infection of the mother by German measles during the first two or three months of pregnancy. It is possible that other virus infections of the

* The classification presented has been found useful for cardiovascular diagnosis It is based primarily on the original paper of White, P D., and Myers, M M: J.A.M.A 77:1414 (Oct 29) 1921

** [illegible]

mother during early germinal layer formation of the fetus may be of importance in the genesis of congenital anomalies of all types.

Rheumatic Involvement of Heart or Blood Vessels: Widespread damage of the heart often accompanies the rheumatic infection, the cause of which is unknown. A filter-passing virus has been suggested as the agent.

Some relationship, allergic or otherwise, evidently exists between rheumatic fever and infection with the hemolytic streptococcus. In its epidemic form it often follows scarlet fever and other streptococcal infections in large groups of susceptible individuals, such as occurred in training areas in World War II.

a. Rheumatic fever (polyarthritis). "Inflammatory rheumatism."

b. Sydenham's chorea; "St. Vitus' dance."

c. Indefinite systemic type ("growing pains," tonsillitis or pharyngitis, gastrointestinal disorders, epistaxis, pulmonary inflammation, and cutaneous or subcutaneous manifestations such as nodules, erythema multiforme, and purpura).

Bacterial Infection (specify bacterium if possible)·

a. Acute (Streptococcus, hemolyticus, staphylococcus, pneumococcus, gonococcus, Bacillus influenzae, meningococcus, some fungus organisms, viruses, rickettsiae, etc.). Such acute infections may involve any or all parts of the heart or may be primarily valvular, myocardial, or pericardial.

b. Subacute (usually nonhemolytic—Streptococcus viridans—type of endocarditis, but including other infections, such as tuberculosis of the pericardium).

Although the difference between the acute and subacute types of bacterial endocarditis is largely a matter of the duration of the disease, the types differ also in the fact that the acute type is usually a complication of an acute septicemia and often affects previously uninjured hearts, whereas the subacute type is much more likely to attack heart valves damaged by rheumatism and to have an unexpected and insidious onset.

Syphilis: This affects most commonly the first portion of the aorta, less often the heart muscle and the arteries of both greater and lesser circulations.

Virus Infection: Virus diseases are, in rare cases, the cause of a true myocarditis. Influenza and mumps, for example, may produce myocardial inflammation, and German measles in the fetus may result in permanent defects in development of the heart. The virus of influenza has been considered responsible for at least some cases of Fiedler's (isolated) myocarditis.

Infestation by Animal Parasites: This includes myocardial involvement in trichinosis and trypanosomiasis, and invasion by flukes and echinococcus cysts. It is very rare in the United States.

Thyroid Disease: *a* Thyrotoxicosis: Long-continued overactivity of the thyroid gland may result in fatigue of the heart from tachycardia and the onset of auricular fibrillation. The hypothesis of a true toxic effect from the abnormal secretion of the gland is unproved.

b. Hypothyroidism. Myxedema has been held responsible in some cases for marked cardiac dilatation and weakness and commonly for low-voltage

curves by electrocardiograph. Cases treated satisfactorily by thyroid medication have shown sometimes striking decrease in heart size by x-rays, and always improvement in the electrocardiographic complexes.

Hypertension: *a.* Systemic: Prolonged hypertension results characteristically in cardiac hypertrophy, chiefly of the left ventricle, and finally failure from fatigue of the muscle with or without the complication of coronary arteriosclerosis.

b. Pulmonary: Factors increasing the tension in the pulmonary circuit, such as mitral stenosis, emphysema, pulmonary fibrosis, and primary disease of the pulmonary vessels (Ayerza's disease), may cause hypertrophy and failure of the right ventricle (*chronic "cor pulmonale"*). *"Acute cor pulmonale"* is caused by massive or multiple pulmonary embolism.

Atheroma and Sclerosis: *a.* Coronary Disease: Degenerative changes of the coronary vessels appear responsible for the common symptom of angina pectoris and their further extension for coronary thrombosis. Slower occlusion with the development of compensatory circulation may result in cardiac weakness or may cause no symptoms.

b. Valvular Sclerosis, the sequel to atheroma or calcareous disease of the valves (chiefly mitral or aortic) results in murmus of regurgitation or obstruction, dependent upon the degree of the process. It is not known how often such changes are preceded by infection of the valves.

c. Peripheral Arterial Atheroma and Sclerosis are causes of vascular but not of cardiac disease

Toxins: *a.* Mineral toxin.

b. Bacterial toxin (diphtheria, focal infection, pneumonia, or other acute disease).

c. Other organic toxins (tobacco, caffeine, digitalis, mushroom toxin, azotemia, etc.).

Neoplasm (Primary or Secondary).

Trauma: Valve rupture, gunshot or stab wounds, contusions, etc.

Irritability: *a.* Neurocirculatory asthenia. "Soldier's heart." "Effort syndrome." This is a common disorder of cardiovascular action in which symptoms of fatigue appear without adequate cause. No organic disease can be discovered in the heart. If not identical with, it is closely associated, in most instances, with an anxiety state

b. Arrhythmias of unknown (? nervous) origin

Cardiac Neurosis: This is a mental attitude toward cardiac disease, with or without organic or functional heart disorder, characterized by apprehension, and related to anxiety states, but rarely to hysteria or other psychoses. The complaints are not consistent with the cardiac findings, or are exaggerated beyond the normal by fear.

Miscellaneous and Indefinite Causes: *a.* Anemia: With marked lowering of hemoglobin from primary or secondary anemia, there are symptoms of breathlessness and tachycardia, with cardiac dilatation and often murmurs of functional type. Changes in heart muscle ("tigering") also occur. In sickle cell anemia there is the added factor of small vascular occlusions of the coronary circuit.

b. Obesity and Fatty Infiltration, "Fatty Heart": The symptoms of

cardiac type in obese individuals are largely due to fatigue and "effort syndrome," but in certain cases large fat deposits in or about the myocardium, especially of the right ventricle, may embarrass its action.

c. "Athlete's Heart": It is doubtful if a normal heart can be injured by physical activity, but in certain cases prolonged exertion, as in long-distance running or ski racing, results in cardiac hypertrophy. Much of what is attributed to "athlete's heart" is, however, due to nervous reactions from competitive effort.

d. Deficiency Diseases: In dietary deficiency diseases, such as rickets and beriberi, myocardial changes have been demonstrated. Excess of such food factors as cod-liver oil and irradiated ergosterol has, on the other hand, been shown experimentally to injure the heart.

e. Scleroderma may become so generalized as to involve heart muscle.

f. Hemachromatosis can produce myocardial changes by foreign body reaction to blood pigment deposition in the heart muscle.

g. Senile: In the absence of obvious coronary disease, advanced age may be associated with changes (dehydration, pyknosis, etc.) of cardiac muscle which attend the general weakening of the body and make it less able to withstand such strains as infection and surgery.

Unknown: Certain obscure cardiovascular conditions still exist which it is only possible to call of "unknown" cause. They should be classified in this way to stimulate further investigation. The most frequently observed is the heart showing unexplained enlargement, often preponderant right ventricular dilatation.

Possible Heart Disease: Cases in which signs or symptoms exist which are not explicable by present methods should, until capable of classification, be called "possible" heart disease.

Potential Heart Disease: This term is limited almost entirely to patients who have had rheumatic infections but who, up to the time of examination, have shown no cardiovascular disease. The term may be applied also to untreated chronic cases of thyrotoxicosis and to syphilitic patients who have received little or no treatment.

STRUCTURAL

Displacement of Heart:

a. Congenital (dextrocardia or ectopia cordis).
b. Acquired mechanically.

Change in Size of Heart as a Whole or of Individual Chambers:

a. Atrophy of heart.
b. Hypertrophy·
  (*a*) Eccentric.
  (*b*) Concentric.
c. Dilatation of heart:
  (*a*) Eccentric.
  (*b*) Concentric.

Myocardial Disease (Acute or Chronic):

a. Congenital defects.
b. Inflammation (diffuse or localized).

c. Fibrosis.
d. Fatty change (infiltration or degeneration).
e. Infarction (ischemic necrosis).
f. Calcification.
g. Neoplasm.

Cardiac Aneurysm.

Cardiac Rupture.

Congenital Anomalies of Cardiac Chambers or Septa.

Endocardial Disease: (Acute or Chronic, involving valves, mural endocardium, papillary muscles, or chordae tendineae):

a. Congenital defects.
b. Inflammation.
c. Sclerosis.
d. Valvular deformity:
   (1) Mitral—insufficiency or stenosis.
   (2) Aortic—insufficiency or stenosis.
   (3) Tricuspid—insufficiency or stenosis.
   (4) Pulmonary—insufficiency or stenosis.

Pericardial Disease (Acute or Chronic):

a. Congenital defects.
b. Inflammation.
c. Effusion (state type of fluid), with or without constriction of the heart itself.
d. Adhesions, with or without constriction of the heart itself.
e. Calcification.
f. Pneumopericardium.
g. Neoplasm.

Vascular Disease:

a. Coronary vessels:
   (1) Congenital anomaly.
   (2) Inflammation.
   (3) Atheroma.
   (4) Sclerosis.
   (5) Aneurysm.
   (6) Embolism.
   (7) Thrombosis.
   (8) Periarteritis nodosa.
b. Aorta:
   (1) Congenital anomaly, especially coarctation and right-sided or double arch.
   (2) Inflammation.
   (3) Atheroma.
   (4) Sclerosis
   (5) Dilatation or aneurysm.
   (6) Embolism.
   (7) Thrombosis.

(8) Medial necrosis, an important finding in cases of dissecting aneurysms of the aorta.
(9) Senile ectasia.

c. Pulmonary artery:
(1) Congenital anomaly.
(2) Inflammation.
(3) Atheroma.
(4) Sclerosis.
(5) Dilatation or aneurysm.
(6) Embolism.
(7) Thrombosis.

d. Peripheral arteries
(1) Congenital anomaly.
(2) Inflammation.
(3) Atheroma.
(4) Sclerosis.
(5) Dilatation or aneurysm.
(6) Embolism.
(7) Thrombosis (thromboangiitis obliterans).
(8) Periarteritis nodosa

e. Disease of veins, capillaries and lymphatics.

Undiagnosed Cardiovascular Disease.

FUNCTIONAL

Normal Mechanism of the Heartbeat and Its Disturbances: This section includes changes in the activity of the heart, which, in many instances, can be accurately analyzed only by the electrocardiograph.

a. Normal rhythm and changes of vagosympathetic origin. Under this heading are the disturbances which occur from an exaggeration of the activity of the nerves responsible for accelerating or slowing the pace-making function of the sinoauricular node.

Normal rate—usually seventy to eighty per minute.

Sinoauricular Tachycardia: This is the response to such factors as exertion, emotion, fever, hemorrhage, asphyxia, thyrotoxicosis, cardiac failure, vagal paralysis, or sympathetic stimulation, which results in a rapid heart rate under control of the normal pacemaker. The rate is between 110 and 175 per minute.

Sinoauricular Bradycardia: This is also a normal response of the heart, by slowing, to such factors as rest, convalescence, jaundice, nausea, or vagal stimulation. The rate is under fifty per minute.

Sinus Arrhythmia· During respiration there is a normal reflex change in vagosympathetic tone which results in an inspiratory quickening and expiratory slowing of the heart called sinus arrhythmia. Rarely, this sinus arrhythmia is not related to respiration.

Sinoauricular Standstill: With marked vagal hypertonia the sinoauricular node may be so depressed that at intervals it does not initiate an impulse. Thus the node is said to be blocked or to be at a standstill.

Wandering Pacemaker: In certain cases the point of impulse formation in the auricle may be shown by electrocardiograph to change its position phasically or irregularly. This appears as an alteration of the auricular (P) wave.

Ventricular Escape (Auriculoventricular Nodal Escape): When the impulses arriving from the sinoauricular node are much slowed or when the auriculoventricular node is irritable, it may "escape" and cause the ventricles to beat at the same time as as the auricles or to precede them.

Auriculoventricular Nodal Rhythm: If the auriculoventricular node becomes irritable or the sinoauricular node much depressed, the former may become the pacemaker for the whole heart and the ventricle may beat constantly before, or synchronously with, the auricle.

b. Disturbances of the pacemaking function:

Premature Beats: Irritable foci in various parts of the heart may initiate single or multiple beats at rates faster than the sinoauricular node, or prolongation of the refractory period with delayed response of certain areas of the heart muscle may result in single or multiple circus movements in one or more directions. The origin of these beats may be:

(α) Auricular.
(β) Ventricular.
(γ) Junctional.
(δ) Unknown

Paroxysmal Tachycardia· If the irritable focus or area of block produces impulses in a connected series, a paroxysm of rapid beats may occur. These may also be:

(α) Auricular.
(β) Ventricular.
(γ) Junctional.
(δ) Unknown.

Auricular Flutter This disturbance is probably due to a "circus movement" or wave of excitation circulating about the great veins at the base of the heart and sending off impulses regularly to the rest of the heart at a speed between 200 and 400 per minute. A regular grade of block usually exists between the auricles and ventricles. The condition may be:

(α) Paroxysmal.
(β) Permanent.

Auricular Fibrillation. This rhythm is a more advanced stage of the circus movement than auricular flutter, and more rapid (average rate in the auricle 300 to 600 per minute) and irregu-

lar. An irregular degree of block exists between auricles and ventricles.

(α) Paroxysmal.

(β) Permanent.

Ectopic Auricular Rhythms of Other Nature Than Paroxysmal Tachycardia, Auricular Flutter, or Auricular Fibrillation: Such rhythms are of obscure mechanism, best explained as under *b* (1) above, and are relatively rare.

Ventricular Fibrillation: This rhythm is not compatible with life for more than a very short time and has been rarely proved by electrocardiograph, although it may be a common terminal state of the heart muscle. Its mechanism may be similar to that in the auricle in auricular fibrillation.*

c. Disturbances of Conduction:

Shortened auriculoventricular conduction time (short P-R interval) may be found in rare cases in association with abnormally wide QRS waves, resembling those of bundle-branch block, in apparently normal individuals subject to attacks of paroxysmal tachycardia or auricular fibrillation.

Auriculoventricular Block.

(α) Partial.

[1] Prolonged conduction time (over 0.2 sec.) between auricle and ventricle.

[2] Occasional dropped beats (failure of the ventricle to respond to every auricular impulse).

[3] High-grade block (such as 2:1, 3:2, 3:1, 4:1, etc.).

(β) Complete: Idioventricular Rhythm: The auricle and ventricle are entirely dissociated, the ventricle beating at a rate usually between 20 and 40.

Intra-auricular Block (produced in experimental animals but not clearly demonstrated yet in man).

Intraventricular Block:

(α) Incomplete bundle-branch block.

(β) Bundle-branch block (right or left). (The present preponderant opinion is that in left bundle-branch block the R wave in Lead I is upright and in Lead III inverted. The reverse applies to right bundle-branch block).

Abnormal Electrical Axis Deviation (Right or Left): Deviation of the electrical axis to the right (inverted R in Lead I and upright in Lead III) is found in the vertical type of heart, as in tall, thin individuals with low diaphragms, and in persons having right ventricular enlargement (due to mitral stenosis, congenital pulmonary stenosis, "*cor pulmonale,*" etc.). Deviation to the left (upright R in Lead I and deeply inverted in Lead III) is found in those with the horizontal type of heart or with

* An almost regular rhythm, intermediate between ventricular tachycardia and ventricular fibrillation, which is comparable to auricular flutter, may be found in paroxysms or prior to the terminal irregular rhythm of ventricular fibrillation.

left ventricular enlargement (due to hypertension, aortic regurgitation or stenosis, etc.).

Faulty Cardiac Efficiency:

a. Congestive failure.
b. Pulsus alternans
c. Neurocirculatory asthenia.
d. Valvular incompetency.
 (1) Mitral.
 (2) Aortic.
 (3) Tricuspid.
 (4) Pulmonary.
e. Angina pectoris, a reaction of the heart to coronary insufficiency.
f. Adams-Stokes syndrome.

Faulty Vascular Efficiency:

a. Hypertension.
b. Hypotension.
c. Vascular spasm (cerebral crises, Raynaud's disease).
d. Vascular dilatation (vasomotor shock).

CARDIOVASCULAR ABILITY

1. Patients with organic heart disease able to carry on ordinary physical activity without discomfort.

2. Patients with organic heart disease unable to carry on ordinary physical activity without discomfort.
 (*a*) Activity slightly limited.
 (*b*) Activity greatly limited

3. Patients with organic heart disease and with symptoms or signs of heart failure when at rest, unable to carry on any physical activity without discomfort.

JOHN T. KING, M.D.
AND
JOSEPH D. B. KING, M.D.

3

The Normal Heart

Introduction: The heart may be considered normal (L. *normalis*, from *norma*, rule or pattern) provided it conforms both in function and structure with the pattern determined from the examination of the hearts of healthy individuals The limits of the norm, or standard, are established through *inspection, palpation, percussion, auscultation*, and by special methods such as *roentgenography, electrocardiography*, determination of *arterial and venous pressures, determination of the circulation time, cardiac output* per minute, *intracardiac pressures*, and *tension of the blood gases*.

Inspection: Inspection of the normal individual usually indicates the absence of such signs of circulatory or cardiac disorder as cyanosis, dyspnea, orthopnea, and edema of the dependent parts. Peripheral pulsation, the degree of which can be delimited for the normal subject only by examination of many healthy individuals, may usually be seen over the carotid arteries, under the outer ends of the clavicles (subclavians), in the episternal notch (innominate), and frequently over the brachial arteries, especially in elderly subjects. Rarely, the radial pulse is visible. While the venous pulse in the neck consists of three waves—*a*, *c*, and *v*—only two are distinguishable customarily with the naked eye, *viz.*, *a* and *c*, deviation from the normal appearance of the jugular waves may throw important light upon the condition of the heart. Certain normal individuals, especially under conditions favoring peripheral vascular relaxation, show capillary pulsation

The precordium is relatively prominent upon the chest wall in about one of each four normal individuals; allowance should be made for this normal deviation from the average chest conformity in estimating the prominence due to such conditions as cardiac hypertrophy, pericardial effusion, aneurysm, or pleural effusion. The *point of maximum intensity* of cardiac impulse (P.M I) may be found in most individuals in the fourth interspace when recumbent, in the fifth when erect. Unless there be an unusual body configuration, the P.M I. in health is not over 9 cm. (3⅗ inches) to the left of the midsternal line, it is usually less, according to the size of the subject. The impulse in this region is usually caused by right ventricular thrust, though the left ventricle forms the anatomical apex of the heart. When the subject assumes the left lateral

decubitus, the heart falls toward the left and the P.M.I. may shift laterally approximately one-half as far as it had been distant from the median line when the subject was supine.

With the patient in the right decubitus, the P.M.I. moves toward the midline, and its distance therefrom is usually about one-half as great as when the patient is supine. Pathological displacement of the P.M.I. may be caused by one or more of various conditions of the heart, mediastinum, pleural, or abdominal cavities. Normally, the impulse may be masked by a thickened chest wall (obesity) or by overlying lung (emphysema). It may be exaggerated in a patient with a thin chest wall, or in the presence of rapid, forceful heartbeat caused by exercise, fever or the use of tobacco or coffee. While the P.M.I. consists of a

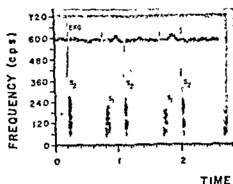


FIGURE 1 Spectral phonocardiograph Normal heart sounds Thirty-two year old man Apex. (From Johns Hopkins Hospital Bulletin 95.90 [Aug] 1954. With permission of Dr Victor A McKusick.)

propulsive thrust, it should be remembered that retraction may occur normally *inside* the P.M.I. and in the *interspace above it.* The impulse itself consists normally of a single systolic forward thrust, there being no visible cardiac movement in diastole.

Palpation: *The initial palpatory procedure should consist of laying* the hand flat against the precordium so as to include the P.M.I., allowing the fingers to conform to the contour of the chest. Such examination throws light upon the general activity and size of the heart and aids in locating the P.M.I., which may be found more accurately through careful palpation with the finger tips. Shocks produced by closure of valves and thrills can be distinguished best by means of the rigid palm of the hand: the fingers should be hyperextended as far dorsally as possible, thus permitting the vibration to be transmitted to the bones of the hand. Following exercise or other stimulus, a normal heart may transmit a certain distinct jar to the hand palpating the P.M.I.; such a phenomenon, however, lacks the truly snapping and clearly cut quality such as is found in mitral stenosis. A tapping impact associated with a normal heart may be felt over the pulmonic valve area in emphysema or other obstructive pulmonary condition; such a shock is synchronous with a second sound. In the presence of hypertension, congenital stenosis of the

aorta or aneurysm, a diastolic shock may be felt at the aortic area, though the heart may otherwise be normal. A true thrill is a vibratory sensation (described by Laënnec as a cat's purr) that is associated with various cardiac diseases; the normal heart may, under excitement, cause a fine vibratory sensation to be transmitted to the palpating hand during systole, but this is rarely sufficiently pronounced to suggest the thrill of cardiac disease.

The Pulse: For purpose of convenience, the radial pulse is examined in preference to that of other vessels, and such examination may throw valuable light upon the condition of the heart. Examination should be made with the finger tips and the following qualities noted: *volume* of the vessel itself and of the pulse wave, *rhythm*, *tension*, *rate* per minute, special characters of the pulse and condition of the *vessel wall;* finally, a comparison of the two radial pulses is made In the consideration of such features of the pulse as volume, tension, and special characteristics, it is well to remember that the volume and tension and many of the distinguishing qualities depend upon (1) the rate of cardiac contraction and the volume of ventricular output with each systole; (2) the degree of elasticity of the arterial walls and the patency of the lumen; (3) the degree of peripheral resistance.

Volume: By volume is understood the apparent size of the pulse wave as it passes the palpating fingers. Volume may be modified in health under various conditions; for example, it may be small under conditions favoring vasoconstriction, such as chilling, or large after exertion or excitement and under conditions favoring peripheral vascular relaxation.

Rhythm: Arrhythmia is found commonly in normal hearts, especially among children. That most frequently encountered consists of acceleration during inspiration, retardation during expiration—sinus arrhythmia; this type may be recognized by its disappearance when the breath is held or after paralysis of the vagus effect by atropine. Arrhythmia independent of respiration is sometimes found, especially in children, and may suggest the complete arrhythmia of auricular fibrillation. Intermittent pulse, due to precocious cardiac systole ("extrasystole") is common among normal individuals; the condition is often most pronounced when the individual is resting (as after retiring) or after excitement, fatigue, or as the result of constipation, distention, pregnancy, or excessive use of coffee, tea, or tobacco. It is common among infants during the first few days of life [10] Precocious systole following each normal contraction of the heart causes bigeminal pulse, provided the premature beats reach the wrist. If the premature contraction occurs after each two normal systoles, or if two premature contractions follow regularly after one normal systole, a trigeminal rhythm is established. As a general rule, a premature contraction of ventricular origin is followed by a pause that is roughly as much longer than the usual diastolic pause as the preceding premature systole was premature. Such a prolonged diastolic pause is spoken of as a "*compensatory pause.*" Auricular premature systoles are followed by an incompletely compensatory or by a normal diastolic rest period.

Tension: The propulsive power of each cardiac ejaculation, together with the resistance of the peripheral vascular bed and the elasticity of the arterial wall, produces a considerable degree of pressure within the arteries. To estimate tension, the pulse is felt with the fingers of both hands; pressure is exerted with the fingers of the proximal hand until the pulse is no longer palpable with the distal hand. The pressure necessary to compress the pulse indicates the arterial tension.

Rate: The rate of the pulse at rest is given as sixty-six per minute for normal men and seventy-four for women, these figures having been derived from more than 2500 observations on about 1200 subjects.[17] The pulse is normally more rapid in childhood, following exercise, or under conditions of mental excitement. Fever usually accelerates the pulse rate to a degree of about ten beats per minute for each degree of fever (F). Paroxysmal tachycardia may occur in an individual with an otherwise normal heart.

Vessel Wall: No examination of the pulse is complete without palpation of the vessel wall. Atheromatous changes are indicated by increased rigidity of the vessel, with tortuosity and palpable calcium deposits, causing a "goose-neck," or nodular vessel.

Percussion: The precordial area is percussed for the purpose of determining the extent to deep cardiac dulness, which marks the approximate border of the heart, and the superficial cardiac flatness, which represents that portion of the heart not covered by lung. In outlining the deep dulness, *mediate* percussion may be used. In this method the percussing or *plexor* finger strikes a finger of the other hand known as the *pleximeter.* Or, *immediate* or *direct* percussion may be employed, the stroke being made with the finger tips directly against the chest wall. Either method is suitable, though indirect percussion is the rule. The pleximeter finger is first laid against the chest wall parallel to the expected border of the heart at a point well outside the probable limit of dulness. The examiner taps the pleximeter finger with the plexor finger, moving the pleximeter finger gradually toward the heart. The percussion note or normal lung resonance becomes duller as soon as the pleximeter finger reaches the cardiac border. The size of the normal heart will be described later in the article on *Roentgenology of the Heart and Great Vessels.* Percussion may not be expected to permit the delimiting of the heart with less than 0.5 to 1 cm. error on each border, left and right. In adults the normal cardiac dulness should not extend more than 10 cm. to the left or more than 4.5 cm. to the right of the midsternal line, though there may be a slight exaggeration of these measurements in individuals whose hearts lie more than ordinarily in the transverse position, due to some such condition as abnormal obesity or distention.

The superficial cardiac flatness can be delimited only through very light percussion. In normal individuals a portion of the heart roughly as large as a silver dollar is not covered by lung; hence, percussion of this part of the precordium produces a perfectly "flat" note. This area begins at the junction of the fourth left rib with the sternum and extends outward and downward in a convex curve.

The relative value of various methods for estimating the position of the left border of the heart has been compared with the clinical localization of the apex by inspection and palpation, with percussion of the left border, and with the roentgenogram (seven foot technic).[15] Comparison of percussion and roentgenogram of the left border in eighty-two cases showed an average difference of 1.5 cm. in measurements of individual cases by the two methods. In certain cases in which x-ray examination *was not practicable, localization of the apex by physical signs was found* satisfactory. In a series of thirty cases, roentgenograms showed the heart's shadow beyond the palpated P.M.I. in nineteen, while in eleven the P.M.I. lay outside the cardiac shadow. Luton[15] concluded that determination of the left border by palpation of the apex and percussion is of value in addition to x-ray measurements.

In infancy and childhood, the left ventricle, about equal in size to the right at birth, becomes approximately twice the size of the right ventricle at the end of the first six years of life.[10]

Auscultation: A binaural stethoscope, fitted with a bell or diaphragm chest piece or with both, is most suitable for the auscultation of the heart. *To be disregarded are noises from without (to exclude which, the ear*pieces must be sufficiently large to fill the external auditory canal completely); skin friction sounds; hair sounds (petrolatum may be applied if necessary to mask friction against the hair); joint sounds from the examiner's fingers or from the patient; muscle sounds (the patient must be relaxed, warm); and the superficial slap of the heart.

Sounds: The sounds of the heart are usually two, traditionally represented by the syllables "lub" for the first and "dupp" for the second sound. Systole, which occupies the period after the first sound and before the second, lasts for approximately 0.37 second, while diastole is about 0.48 second in length, varying with the heart's rate. A third sound, which *has been found in 50.9 per cent of young adults,*[21] *was present among* healthy soldiers in 23.6 per cent [12] This sound is soft, low-pitched, and is best heard with the subject supine or in the left lateral decubitus. It is most clearly audible at the P M.I. or just inside, and is associated in some manner with ventricular filling (end of "active diastole," about 0.13 second after the beginning of the second sound).

The first sound at the apex may be exaggerated as a result of exertion, fever, and nervousness and is normally louder in young people than in older. The pulmonic second sound is usually louder than the aortic before twenty years of age; between twenty and thirty, the predominance of one sound over the other is about equally frequent; after thirty, the second aortic sound is usually louder.

Reduplication of either first or second sound may occur in health. Reduplication of the first is uncommon (about three per cent) and is apparently due to impact of the heart against the chest wall; it usually disappears or becomes less marked when the subject lies upon the back. Such reduplication consists of two rather loud sounds of approximately equal intensity. At times a normal presystolic sound may be heard;[2] the sound, usually below the level of audibility, follows shortly (0.02 second) after

the beginning of auricular contraction and precedes the first sound by about 0.01 second. It may be associated with "tension of the ventricular walls." Reduplication of the second sound is common in health, especially during deep respiration. As a rule, it is probably due to a retardation of right ventricular emptying, with delay in closure of the pulmonic as compared with that of the aortic valve.

During World War I, in the course of examination of soldiers on active duty, King[12] found various auscultatory phenomena, their frequency of incidence being shown by the table that follows:

TABLE 1

AUSCULTATORY PHENOMENA OF 500 SUPPOSEDLY NORMAL HEARTS

	No. Cases	*Per Cent*
Third heart sound	118	23 6
Reduplication of first sound at apex	16	3 2
Systolic apical click	2	0 4
Systolic murmur at apex present in recumbent posture, absent in erect posture	65	13 0
Cardiorespiratory systolic murmurs limited to inspiration:		
At apex	16	3 2
At conus arteriosus	4	0 8
At aortic area	3	0 6
Cardiorespiratory systolic murmurs present in both inspiration and expiration:		
At apex	13	2 6
At conus arteriosus	5	1.0
At aortic area	2	0 4
Accidental systolic murmurs:		
At conus arteriosus	70	14 0
At aortic area	31	6 2
Cardiorespiratory diastolic murmurs:		
Near aortic area	3	0 6
Near conus	1	0 2
Near apex	0	0 0
Extrasystoles	9	1 8
Reduplicated second sound at conus area	23	4 6

Systolic Click: Occasionally a sharp, superficial, dry, clicking sound is heard at or near the P.M.I. It may occur at any time during systole. While it is not affected radically by inspiration, it does occasionally disappear when the subject is supine, which lends strength to the writers' impression that it is an accidental extracardiac phenomenon. Though it may be found rarely after acute pericarditis, it has no apparent significance.

Sternal Crunch: Either heart sound or both of them, may be associated with a superficial crunching sound when the stethoscope is placed at the lower left border of the sternum. This has been said to be due to friction

of the heart against certain superficial structures, notably the pericardiodiaphragmatic ligament.[1] This sound may be prolonged into a squeak closely resembling a murmur and may be mistaken for the murmur of mitral insufficiency. The crunch is heard best when the subject leans forward and its intensity is decreased, as a rule, when the supine posture is assumed; it may disappear altogether in this posture. The fact that the sternal crunch is at times quite loud over a dilated or hypertrophied heart has led some observers to the fallacious assumption that the sound is an indication of heart disease; however, the frequent occurrence of the crunch among perfectly normal individuals leaves no doubt that it is of *no pathological significance. The crunch may also be particularly intense* in individuals with "flat" or "funnel" chests.

Normal Murmurs: An apical murmur heard with the subject in the recumbent posture is not uncommon; its prompt disappearance when erect places the murmur at once among normal cardiac phenomena. It gives the distinct impression of originating within the heart; the question has been raised of whether it may be due to a real but slight mitral incompetence that is to be considered physiological in certain individuals.[22]

Cardiorespiratory murmurs, limited to inspiration, may be heard at the apex or base, outside or just inside the apex, and in the left lower thoracic region behind. They are caused by impingement of the heart as it moves in systole against the lung, causing a systolic accentuation of the inspiratory breath-sound. They are apt to be loud over the lingula pulmonalis, just inside the cardiac apex, and are usually best heard with the subject erect. They may disappear altogether when the supine position is assumed. As a rule, they disappear when the breath is held in inspiration; if they do not disappear, they are sufficiently modified by this procedure to allow recognition Any murmur limited to the inspiratory phase of respiration should be considered to belong to the category of cardiorespiratory murmurs.

The examiner should observe the precaution to have the subject hold the breath after inspiration through several cardiac cycles; in certain individuals the murmur may persist temporarily after full inspiration but will fade away if the lungs are kept full over several heart beats.

Graphic Analysis of Heart Sounds: Further refinement of the graphic representation of heart sounds is provided by the "spectral phonocardiograph"[16] (see Figure 1). The sounds are picked up by a microphone applied to the precordium and pass through a battery of filters, each of which is tuned to a particular frequency pass-band. Each filter lets through only energy in its particular frequency band. In turn each filter activates a small light behind a rotating phosphorescent belt. The record has the time dimension as the abscissa and frequency spectrum as ordinate. Intensity is indicated by the blackness of the mark.

The "spectral phonocardiograph" thus obtained is the application to phonocardiography of the sound spectrograph, or "visible speech." Its advantages over the oscillographic phonocardiograph are that is has distinctive patterns, permitting a precise physical definition of the numerous adjectives used in describing heart-sounds and murmurs. It promises fu-

ture value in the teaching of phonocardiography and in objective differentiation of sounds and murmurs which have different pathologic significance but which may sound identical to the ear.

X-ray Measurement of Heart: It is not necessary to go into details or technic of this method of arriving at the size of the heart, except to say that measurements of the normal hearts that are to be discussed are derived from either teleroentgenograms or orthodiagrams. They indicate, therefore, the actual size of the heart as it functions.

In attempting to decide whether or not a heart is of normal size, it is well that the examiner bear in mind certain peculiarities of the normal heart. For example, the right auricle undergoes rapid hypertrophy during the first six weeks of life; allowance for this natural phenomenon must be made before diagnosis of auricular hypertrophy is made.[10]

A very interesting study of the child's heart derived from yearly x-rays of 246 normal school children during seven school years shows that the average median diameter of the right side of the heart increases steadily with age in children from two through thirteen years of age, being greater in girls than in boys. Before the age of seven, the girl's heart is larger than the boy's, after the age of eleven the condition is reversed. The transverse width of the heart varies between 7 and 8.2 per cent of the height of boys from two through thirteen years of age, and from 6.9 to 8.4 per cent of the height of girls of corresponding ages. There was found to exist a closer correlation between the size of the heart and height than between the size of the heart and age. Approximately one-third of the heart lies to the right of the midline in childhood. The transverse diameter of the heart is approximately one-half that of the width of the chest, and there is no change in this relationship with increasing age or height.

A schedule of the size of the normal heart in childhood follows:

TABLE 2

Age	*Transverse Measurement, Cm*	*Age*	*Transverse Measurement, Cm*
First quarter year	5.3	Third year	7.8
Second quarter year	6.1	4 to 5 years	8.0
Second half year	6.7	6 to 7 years	8.4
First year	7.2	8 to 10 years	9.1
Second year	7.2	11 to 14 years	9.6

In obese individuals or as a result of such conditions as ascites and abdominal tumor, the diaphragm is usually rather high, causing the heart to assume a relatively transverse position; measurements of a heart of normal size in this position may be greater than those of normal hearts in the usual position. The relatively transverse heart also shows a tendency toward filling the left cardiohepatic angle. A heart of normal size may be displaced as a result of scoliosis, lateral posture, hydro- or pneumothorax, and various other conditions. Hence the measurements of the heart in either direction if of no significance unless the general condition of the patient at that time is taken into consideration.

In this section, the size of the heart will be considered as it is indicated by the maximum size from the midline to the left (M.L.) and to the right (M.R.). The greatest transverse diameter will be considered the sum of the two.

Important data have been brought out bearing upon the relation of the transverse measurement of the heart with that of the chest. The following relations exist:[8]

TABLE 3

$\frac{\text{Transverse heart measurement}}{\text{Transverse lung measurement}}$	$= \frac{1}{1.9}$	in children
$\frac{\text{Transverse heart measurement}}{\text{Transverse lung measurement}}$	$= \frac{1}{1\ 92}$	in 20-year-old subjects
$\frac{\text{Transverse heart measurement}}{\text{Transverse lung measurement}}$	$= \frac{1}{1\ 95}$	in 30-year-old subjects

The figure for the normal heart may be as high as 1:1.99. Chest *measurements were made from the ribs.*

The width of the heart, as a general rule, should not be greater than one-half that of the chest,[6] but there is found in the literature evidence for a certain latitude in applying the rule. Certain roentgenologists feel that the normal heart may measure as much as fifty-five per cent of the width of the chest in individuals of peculiar body configuration.

The actual size of the adult heart, at least as far as can be estimated from a large number of measurements upon the hearts of normal soldiers, has been shown to be as follows:[18]

TABLE 4

Height Cm.	*Cases*	*M R Cm*	*M.L Cm*	*L D Cm*	*B D. Cm*	*Area Sq Cm*
155 to 164	18	4 0	8 3	13 3	9.9	111
165 to 174	174	4 1	8 5	13.1	10 2	118
175 to 187	185	4 3	8 7	14 2	10 7	122

M L · Distance from the midline to the most distant left border
M R · Distance from the midline to the most distant right border
L D · The maximum long diameter, measured from the right auricular notch to the most distant apical border
B D : The maximum broad diameter, measured at right angles from the long diameter to the most distant border above and below

Cardiac Output: According to Grollman[9] the cardiac output is generally acknowledged to be the most important function descriptive of the circulation. It is defined as the output of the left ventricle in liters per minute. The estimation of cardiac output, at rest and especially during effort, yields invaluable information in delineating the normal from the abnormal heart.

Methods based on the Fick principle

According to the Fick priniciple:

Cardiac output equals:

$$\frac{O_2 \text{ intake (ml. per min.)}}{\underset{\text{(Vol. \%)}}{\text{Arterial blood } O_2 \text{ content}} - \underset{\text{(Vol. \%)}}{\text{Mixed venous blood } O_2 \text{ content}}} \times 100$$

OR Cardiac output equals:

$$\frac{CO_2 \text{ output (ml per min.)}}{\underset{\text{(Vol \%)}}{\text{Mixed venous blood } CO_2} - \underset{\text{(Vol. \%)}}{\text{Arterial blood } CO_2}} \times 100$$

Direct Fick Method: By means of right heart catheterization, introduced in this country by Cournand, samples of mixed venous blood can be obtained directly from the right auricle or ventricle. As a result of this advance, this so-called "direct Fick" method is at present the most widely accepted. Disadvantages of this method include the psychic effect on the cardiac output of the subject by introducing a catheter in the arm, and the difficulty of satisfactory exercise performance with the apparatus in place.

The cardiac index, or cardiac output per square meter of body surface, determined by the method of right heart catheterization, was found to average, *under basal conditions, 3.12 liters per minute for thirteen normal* males, 3 73 liters per minute for eleven hospitalized males with normal circulation, and 2.99 liters per minute in six hospitalized females with normal circulation.[4]

Stroke volume can be computed by dividing the cardiac output per minute by the cardiac rate.

Indirect Methods Based on the Fick Principle: These methods do not require catheterization of right heart. Here the assumption is made that the volume of gas absorbed by inhalation is a function of the pulmonary blood flow, *hence cardiac output. Foreign gases, chiefly acetylene,*[9] *ethyl* iodide,[20] and nitrous oxide[13] are employed.

Other Methods. *Dye Dilution Methods:* The principle here is that the degree of dilution by the blood stream of an injected dye will be determined by the blood flow. Dye is injected into a vein, and multiple samples of blood are drawn seconds later from the femoral artery. From the concentration of dye in these samples a dye dilution curve can be described. Cardiac output may be then determined from the amount of dye injected, the duration of the curve and the concentrations of the dye in the arterial samples.[7] *Results with the dye injection method are more* or less similar to those obtained by the direct Fick method. A comparison of these two methods revealed a scatter "no greater than would be expected when known inaccuracies in both methods are considered."[11]

Methods Employing Sphygmomanometry: Starr[19] has provided the clinician with a formula for estimating cardiac output from simple bedside measurements. The formula, derived from cadaver experiments in which cardiac systole was simulated, is as follows:

Stroke volume = 93 + 0.54 pulse pressure (auscultatory) —0.47 diastolic pressure (auscultatory) —0.61 age,

diastolic pressure being considered the point of muffling of sounds.

Circulation Time: The circulation time, or circulatory rate, may be measured by a number of simple tests:[3]

Arm-to-Mouth Time: Sodium dehydrocholate (Decholin) 2.0 cc. is injected into the antecubital vein. The end-point is a bitter taste experienced by the subject. Average normal circulation time by this method is 18 seconds.

Arm-to-Lung Time: In this test ether (0.5 cc.) in saline (1.5 cc.) is injected into the antecubital vein. End-point is the odor of ether on the subject's breath. The circulation time in this test is six seconds

Arm-to-Brain Time: Papaverine affords a suitable method of estimating arm to brain circulation time. Pointing out that cyanide probably exerts its typical effect in the carotid sinus, the authors report that the action of papaverine is slower and probably indicates the arm to respiratory center time or the time required for papaverine to affect the vessels of the brain. The end point, after injection into an antecubital vein, is a sudden deep inspiration in which the abdominal muscles are employed; there may also be a sigh or a gentle exclamation. This is followed by flushing, dizziness, sense of heat, and tachycardia. Forty mg. of papaverine are employed in the test, the injection being given within one second. Normal values for forty-one men and nine women without evidence of circulatory disease were 15.4 to 27 seconds (average 20). While the reaction time is distinctly slower than that with other methods, the papaverine test has the advantage that the observation can be made, without additional injection, in a patient who is receiving intravenous therapy with this drug.

On the whole, the decholin test seems to have gained widest favor, and is in common use without serious complications.

Intracardiac Measurements: By the technic of intracardiac catheterization direct measurements of pressures within the right heart are provided. In addition, partial pressures of respiratory gases can be determined from blood samples withdrawn from the cardiac chambers[5] (Table 5).

TABLE 5

OXYGEN CONTENT OF BLOOD AND PRESSURES IN PULMONARY ARTERY, RIGHT VENTRICLE, AND RIGHT AURICLE OF CONTROL GROUP OF PATIENTS (FROM DEXTER, L. *et al.*[5]).

Patient No	*Diagnosis*	*Age*	*Oxygen Content (Vol Per cent)*			*Pressure (mm. Hg)*			*A-P Diameter of Chest (cm)*
			Pulmonary Artery (Main Stem)	*Right Ventricle (Mid Portion)*	*Right Auricle (Upper Portion)*	*Pulmonary Artery*	*Right Ventricle*	*Right Auricle*	
1	No disease	15	14 6	14 4	14 4	32/12	32/6	6	15 5
2	No disease	17	15 3	14 8	15 3	20/8	20/0	0	16 0

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CHARLES C. WOLFERTH, M.D.
AND
ALEXANDER MARGOLIES, M.D.

4

Heart Sounds

Introduction: In the consideration of sound, it is necessary to bear in mind that there are two components involved, *viz.*, the actual vibrations and the sensation produced by these vibrations. Students of sound may be interested primarily in either or both. When the clinician practices cardiac auscultation, he is concerned with the auditory sensations produced by the vibrations. If, on the other hand, he registers the sounds by means of a sound recording apparatus, he interests himself in the physical characteristics of the vibrations. In the use of terminology it is necessary to bear these distinctions in mind. Thus, intensity and loudness of a sound are not interchangeable terms, although, as intensity increases or decreases, loudness varies in the corresponding direction. The human auditory apparatus has so accommodated itself to its environment that tremendous changes in intensity may be reflected by what seem to be much less marked changes in loudness Furthermore, the sensation of loudness of a sound may be modified by stimuli immediately preceding it. Thus, recorded vibrations do not faithfully mirror what is heard on auscultation.

The knowledge concerning heart sounds which had accumulated from the time of Laennec until 1907, when Einthoven published his string galvanometer method of registering sounds, was based almost entirely on auscultatory studies, since previous attempts at registration had not been very successful. The literature covering the period during which this knowledge was in the making reveals much inaccurate observation and reasoning responsible for certain misconceptions still widely held today. On the other hand, the work of some of the great masters of auscultation, notably Potain, must command our admiration.

Sound registration has made possible accurate study of the time relations of heart sounds with other cardiac events, thus furnishing data essential for the understanding of the mechanism of production of the sounds. Attempts have also been made to study the physical characteristics of the vibrations, but because of the imperfections of the methods of registration available, great caution must be observed to avoid error. In spite of these limitations, Einthoven,[1] Lewis,[2] Wiggers,[3] and others have been able to make notable contributions to the understanding of heart sounds.

Most of the important heart sound registration studies have been made by physiologists who were not primarily interested in the clinical applications of the method, although many facts of clinical importance have been demonstrated. There remain wide gaps in our knowledge regarding the mechanisms of sounds produced by cardiac action in normal and diseased hearts. This discussion is an attempt to bring the student and the practitioner abreast with current knowledge of the subject.

The unsatisfactory state of the art of auscultation as it is generally practiced becomes obvious to anyone in a position to review the findings of various examiners of the same patients and the differences in the conclusions reached following such examinations. Nevertheless, it may be stated that nearly all these differences of opinion are unnecessary and due to the fact that many physicians have not rigorously trained themselves in the art of auscultation. To acquire this training, no superiority of senses is needed. Reasonably normal ability to concentrate, normal hearing, a normal sense of timing and a normal appreciation of such qualities of sound as pitch and loudness are about all the qualifications that are necessary. Most medical students and practitioners possess all of them. Many errors in auscultation are those of omission, due to such factors as lack of thoroughness of examination or unfamiliarity with certain types of sounds. Most students are apt to miss the low-pitched murmur of mitral stenosis until their attention has been called to this sound and they have become thoroughly familiar with its characteristics. As soon as their receptor mechanisms are trained, they develop proficiency in the recognition of the murmur. Today, perhaps only a small minority of even well-trained physicians recognize with any approach to accuracy such a common and important auscultatory finding as gallop rhythm. Nevertheless, gallop rhythm is nearly always easy to detect after one has become familiar with it. The important steps in acquiring skill in the art of auscultation are (1) to acquire familiarity with the various sounds and murmurs and their characteristics; (2) where to listen for them; (3) what maneuvers may be employed to elicit or accentuate sounds and murmurs, and (4) to educate one's sense of timing. One of the most frequent errors of interpretation of sounds is due to faulty timing.

What value sound registration may possess for further clinical research would be difficult to predict. There is one field, however, in which sound registration studies have a real value. Their comparison with auscultatory findings constitutes an excellent training method for sharpening the auscultatory faculty. Recently, there has been a great reawakening of interest on the part of clinicians in the study of heart sounds, doubtless due in part to improvements in methods of registration.

THE FIRST HEART SOUND

It has been established that the first heart sound is related to an early stage of ventricular contraction. Einthoven[4] believed that the sound and electrical disturbance in the ventricle begins simultaneously. Wiggers,[5] however, failed to confirm Einthoven's observation and believes that the beginning of the electrical disturbance precedes the sound.

The assumption is generally made that the first sound heard over the precordium is almost wholly left ventricular in origin, but studies of asynchronous contraction and splitting of the sounds, such as occur in ventricular extrasystoles and bundle branch block, suggest that the right ventricle sometimes contributes a larger share than is generally believed.[6] Although the right ventricle usually contains much less muscle than the left and by reason of lower pressure probably does not contract so forcibly, nevertheless, the position of the heart is such that sounds produced in the right chamber may be better transmitted through the anterior chest wall than those from the left side.

It is assumed by many writers that mitral and tricuspid valve closure are concerned in the sound production and it is customary to designate certain comparatively short high-pitched first sounds as having a "valvular quality." It is probable that the valves close early in systole while intraventricular tension is still low. There is at present no convincing evidence to indicate whether or not valve closure contributes vibrations to the first sound. The practice, therefore, of describing certain first sounds as "valvular" is open to criticism, unless it be clearly understood that the term has no reference to the mechanism of production.

A factor which may sometimes contribute to the production of the first sound as heard over the precordium is the sudden pressure of the contracting apex against the chest wall. The importance of this factor is also difficult to evaluate, but it is of interest that in cases with a sharp apex impulse, the loudness of the first sound may sometimes be diminished by firm pressure with a finger over the area of the impulse.

In discussing the mechanism of production of the first heart sound, Wiggers[3] has stated that sound intensity varies directly as the systolic *tension developed within the ventricles, and there is good reason to* believe, with the tension developed during the isometric period of systole (the time between the beginning of ventricular systole and opening of the semilunar valves). A comparison of the time relationships of the first heart sound and the dynamic events of the heartbeat demonstrates clearly that the major portion of the first heart sound occurs before the semilunar valves have opened. The sound would, therefore, appear to be synchronous with at least part of the period of rising tension within the ventricles. A study of the clinical material, however, does not support the view that the intensity of the sound varies according to the actual amount of elevation of intraventricular pressure during this period. Evidence bearing on this point may be summarized as follows:

1. It has been shown that the marked variations of intensity of the first heart sound usually present in complete heart block depend on the time relations of auricular and ventricular contractions.[7] These changes in sound intensity are independent of changes in pulse volume (Fig. 1). Similar changes in the first sound are also observed in other disturbances of cardiac mechanism in which varying auriculoventricular relationships occur, such as ventricular escape, extrasystoles (both auricular and ventricular), and paroxysmal tachycardia.[8] It is easily demonstrable in the case of extrasystoles that beats with small pulses may have a first sound

either decidedly louder or fainter than the adjacent normal beats, depending in part but not entirely upon the auriculoventricular relationship (Fig. 2).

2. In mitral stenosis there is frequently a very sharp loud first sound irrespective of the blood pressure or the vigor of the heartbeat. Con-

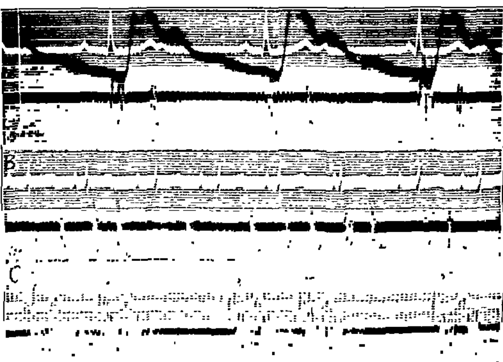


FIGURE 1 *A*, Complete heart block As the P-R intervals decrease the first sound becomes louder. The pulse remains about the same irrespective of the loudness of the first sound *B*, Ventricular escape and minor grade heart block with variations in loudness of the first heart sound depending on the As-Vs intervals The first sound is loud when the P-R interval is comparatively short *C*, Variations of the first sounds in auricular fibrillation. In the second and fourth beats which are relatively premature, the vibrations of the first sound are much larger than in the third and fifth beats The second sounds in these four beats show little variation High pitched systolic and low pitched diastolic murmurs are present

versely, in mitral regurgitation, the loudness of the first sound tends to be diminished and, in many cases, the sound cannot be heard even at the apex, though cardiac contraction may be carried out in a vigorous manner and the pulse volume be good.

Observations of this type suggest that some other factor must be concerned in determining the intensity of the first heart sound. Possibly the rapidity of rise of intraventricular tension may be more important than the height of tension developed. The point may be illustrated in the following way: If a string is suddenly snapped taut, a sound may be produced even though the tension is low, but if the application of tension is more gradual the sound will be less with the same or even greater tension. The hypothesis as applied to the first heart sound, however, would be difficult to establish, since no method is available by which the

rapidity of intraventricular pressure rise can be determined except in experimental animals. There are some facts, however, which would seem to favor the hypothesis.

(1) In the case of mitral regurgitation, there may be retardation of the development of intraventricular tension due to leakage of blood

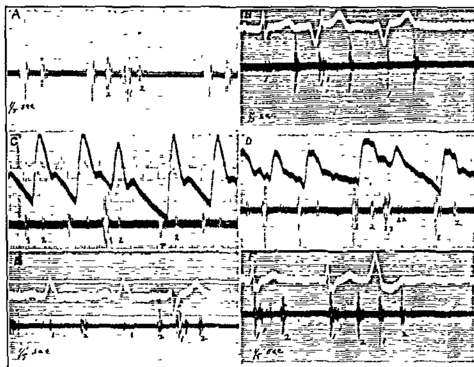


Figure 2 *The heart sounds in extrasystolic beats* *A*, The first sound is represented by about the same pattern of vibrations in the extrasystoles as in normal beats The second sound in the extrasystole shows small vibrations and the interval between the first and second sounds is decreased *B*, The first sounds are louder in the extrasystoles than in the beat with the prolonged P-R interval and normal type of ventricular complex. In the first extrasystole the first sound

(and therefore leakage of pressure) back to the left auricle during the early part of systole. Wiggers and Feil[9] have shown that the amount of this regurgitation must be small Nevertheless, their curves of intraventricular pressure appear to show that the gradient of rise during the isometric period is less steep when regurgitation is present. In mitral stenosis, on the other hand, rigidity of the valve leaflets which holds them near a position of closure may favor the rapid development of intraventricular tension (2) The marked differences in the first sound associated with changes in auriculoventricular relationships may be due

to the effect of auricular contraction on the position of the A-V valves. It has been demonstrated by Dean[10] that auricular systole causes marked changes in the position of the A-V valve leaflets. Considering this fact it logically follows that if the leaflets were near a position of closure at the beginning of ventricular contraction, intraventricular tension might be expected to rise more rapidly than if the leaflets were more widely opened so that some regurgitation of blood (and therefore pressure) back into the auricles occurred before valve closure.

There is a widely held clinical view that a loud first sound signifies a strongly acting heart, and a weak sound, a feebly acting heart. Wiggers[3] has supported this view, stating that the relative intensity of the sounds may be safely used as a clinical index of the vigor with which the ventricular contraction is carried out. There is some clinical evidence in favor of it: (1) In hearts with small ventricles showing quick wide excursions under fluoroscopic examination, the first sound tends to be loud and sharp. On the other hand, when the ventricles are enlarged and their excursions insignificant, the sound is frequently faint. (2) During conditions of marked depression of the circulation, such as are produced by surgical shock or severe infection, the first sound may be faint but with the onset of recovery and restored cardiovascular function, it becomes much louder.

On the other hand, the effects of A-V time relationships and disease of the mitral valve on the first sound do not support the view that the relative intensity of the first sound may be safely used as a clinical index of the vigor with which ventricular contraction is carried out, unless these factors are excluded. The auriculoventricular relationships and the function of the A-V valves in many cases are far more important in determining the loudness of the first sound than the actual vigor of contraction. Even in auricular fibrillation, in which the variable of auriculoventricular relationships does not have to be considered, the loudness of the first sound does not always vary in the same direction as the actual strength or force of the beat.[8] Thus, in some cases there may be no significant change in the relative intensity of loudness of the first sounds, even though great differences in successive pulse waves are present. This is most likely to occur in mitral stenosis. In other cases, premature beats with small pulse waves may have first sounds either louder or fainter than the less premature beats.

In the paragraphs above, the thought in mind has been chiefly the significance of variations of the first heart sound as they apply to single cases. When an attempt is made to evaluate the first heart sounds in different cases, there are not only the factors mentioned above to deal with, but certain others in addition Thus, lack of synchronism in its components may markedly modify the intensity of the sound. So-called reduplication or splitting is very common both in healthy and diseased hearts. Registration of such sounds frequently shows clear-cut separation of two elements.[6] The cardiodynamic studies of Katz[11] show that perfect synchronism of contraction of the two sides is the exception rather than the rule, and studies of sound records would appear to bear out

this view. When slight asynchronism is present but not enough to produce actual separation of two components, there may be merely prolongation of the sound and lessening of its intensity. This may cause the so-called muffled first sound. It is present in many cases in which there is no reason to regard the vigor of cardiac contraction as diminished.

Among other factors to be considered are differences in shape of the chest wall, variations in the position of the heart, the varied composition and thickness of overlying tissues and their damping effect on the sound vibrations transmitted through them, and, finally, the extent of abdominal distention, especially the amount of gas in the stomach and its effects on the position and action of the heart and the resonance of the sounds.

Study of the first heart sound in over 500 cardiovascular cases[12] with special reference to the loudness of the sound yielded the following results: In general, youth, small heart size, thin chest wall, thyrotoxicosis, mitral stenosis and hypertension tended to be associated with a loud first sound. Old age, thick chest wall, bradycardia, emphysema, shock, pericardial effusion, mitral regurgitation, and myocardial disease, especially myocardial infarction, tended to be associated with a faint first sound The above correlations were slight, however, as compared to the correlation between loudness of the first sound and duration of the P-R interval. Thus when the P-R interval was in the short normal range (0.12 to 0.14 second) the first sound tended to be loud; when the P-R interval was in the long normal range (0.18 to 0.20 second) the first sound tended to be faint; when the P-R interval was in the intermediate range (0.15 to 0.17 second) the first sound tended to be of medium loudness. In persons with healthy hearts this correlation is remarkably good It is exceptional to find, in the absence of heart disease, a loud first sound and a long normal P-R interval or a faint first sound and a short normal P-R interval.

In view of the considerations stated above, the clinician must be cautious in attempting to draw conclusions from the character of the first heart sound regarding the condition of the heart. He must take into account the various factors which are known to influence the loudness of the first sound.

In the above discussion no emphasis has been placed on the quality or timbre of the first heart sound, although clinicians can scarcely fail to be impressed by the probability that they are significant. A comparison of sound records made in different cases shows decided variations in the principal as well as the minor vibrations of first heart sounds The imperfections of present methods of registration do not justify attempts to study the finer characteristics of the sounds. Although there are many exceptions to the rule, the tendency is to associate a so-called "booming," or "muscular," low-pitched and prolonged first sound with hypertrophied ventricular muscle, such as may occur in arterial hypertension, aortic insufficiency, or in the hearts of athletes. A short, sharp, higher pitched first sound is suggestive of mitral stenosis, hyperthyroidism or the effort syndrome. To what extent alterations in the character of the sounds, such as those mentioned, may be due to differences in muscle mass,

thickness of fibers, extent or rapidity of their contraction, and the accompanying intraventricular pressure changes remains unknown.

Splitting of the First Heart Sound: It is obvious both from careful auscultation and analysis of sound records that the first heart sound is a complex phenomenon. It has long been recognized that at least two major components are often concerned in its production. At times these two components are sufficiently widely separated so that two distinct sounds may be recognized. This phenomenon has been called splitting or reduplication of the first heart sound. Comparatively little work has been reported, concerning the cause or nature of this splitting. The two chief views have been as follows: (1) The two components are of different origin. One is "muscular" and due to movement of interlacing cardiac fibers as they contract. The other is "valvular" and due to forcible closure of the auriculoventricular valves in the early stages of contraction. This hypothesis, which is the one most widely held, has led to the description of the first heart sound as predominantly "muscular" or "valvular" in quality. (2) The second view holds that the mechanism of production of the two components is similar in nature, one component being produced as a result of left ventricular contraction and the other as a result of right ventricular contraction. A necessary corollary to this view is that when the sound is split there must be asynchronism in the action of the two ventricles in at least some part of the early stage of contraction. Although this hypothesis received some support in the earlier literature, it was discarded for a long time because the idea that the ventricles could exhibit asynchronism in contraction was regarded as untenable.[13] However, during the past few years, evidence has been produced to indicate that even healthy hearts may exhibit at least sight asynchronism in contraction of the two ventricles. Furthermore, evidence is available to suggest that one major component of the first sound may arise in the left ventricle and one in the right ventricle.[6]

A certain amount of confusion has arisen in the literature because of the lack of a satisfactory definition as to just what constitutes the first heart sound. Registration of the heart sounds reveals the fact that occasionally there may be as many as three separate groups of major vibrations in the time zone during which the first sound is supposed to occur. Likewise, groups of minor vibrations are frequently observed. At the present time any definition as to what constitutes the first sound must be regarded as arbitrary although definition is necessary if the subject is to be discussed without confusion.

Sound tracings frequently show minor vibrations resulting from auricular contractions which are not detected on auscultation. These vibrations may be regarded as the prototype of presystolic or auricular gallop sounds which will be discussed later. As a rule, they begin in the range of 0.08 to 0.14 second after the beginning of the P wave. Thus, if the P-R interval is in the low normal range the sound vibrations may coincide with the beginning of the Q-R-S complex and at times the beginning of the Q-R-S complex may actually precede the beginning of

these vibrations. If the disturbance is great enough to produce audible sound, the occurrence of this sound preceding the sound caused by ventricular contraction may give the impression of splitting of the first sound. In our opinion there are good practical reasons for not including this sound of auricular origin as a part of the first heart sound. As a rule it begins even before the first electrical manifestation of ventricular activity and under these circumstances can be recognized clinically as "presystolic." Furthermore, this sound is nearly always a manifestation of gallop rhythm and should be recognized as such because of the important clinical significance of gallop rhythm. The significance is apt to be missed if this grouping of sounds is called splitting or reduplication of the first sound.



FIGURE 3 Phasic respiratory splitting of the first heart sound Beat two shows some merging of the two components, beat three shows them side by side producing a so-called muffled or prolonged first sound, and beat five shows a separation of the two components

A short, high-pitched, clicking or knocking early systolic sound (to be discussed later) is occasionally heard over the precordial area and is usually loudest in the second, third, or fourth interspace just to the right or left of the sternum. The occurrence of this sound following the first heart sound is apt to furnish an auditory impression of reduplication. However, its area of maximum intensity, its clicking or knocking quality and its occurrence at the instant of ejection of blood from the heart mark it off from what is ordinarily regarded as the first heart sound.

In the normal healthy individual, the first heart sound may be heard as a single or double sound. Variations associated with the phases of respiration are not uncommon, particularly in young people (Fig. 3). Thus in a succession of beats extending through a complete respiratory cycle one may find single short sounds, prolonged so-called muffled or impure sounds and splitting into two distinct components

A study of the time relations of single first heart sounds shows that the major vibrations usually begin in the range of 0.03 to 0 08 second after the beginning of the Q-R-S complex of the electrocardiogram, and before ejection of blood Thus, the sound occurs during the isometric period of ventricular contraction

For the purposes of this discussion, therefore, we define the first heart sound as a sound or grouping of sounds heard in the precordial area, associated with the act of ventricular contraction and occurring during the isometric phase of contraction of the ventricle from which each

component of the sound arises. The reason for such a definition is to exclude sounds due to auricular contraction and those associated with the beginning of ejection from the ventricles, either of which, occurring in close association with the first sound, may be mistaken for true reduplication.

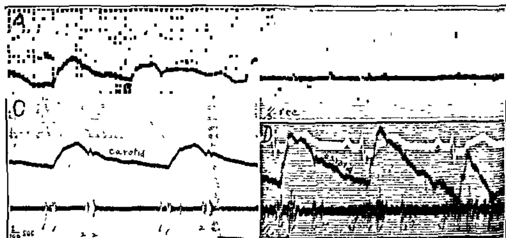


FIGURE 4 The relationship of split sounds to left ventricular ejection. *A*, Electrocardiogram and carotid pulse *B*, Electrocardiogram and sounds Both *A* and *B* were made in a patient with left bundle branch block and ventricular extrasystoles Despite the prematurity of the extrasystole (which tends to cause delay in ejection) and the smallness of its pulse (which slows its velocity) the premature pulse falls relatively earlier than those of the supraventricular beats In the beats showing left bundle branch block both components of the split first sound precede the carotid upstroke In the extrasystoles, the first component precedes and the second follows the carotid upstroke The vertical lines in *B* indicate the times of the carotid upstroke *C*, Split first and split second sounds in left bundle branch block Both components of the split first sound precede the beginning of the carotid pulse The second component of the split second sound begins just ahead of the carotid incisura and represents aortic closure *D*, The relations between ejection and split first sounds in right bundle branch block The first component of the first sound preceded the carotid upstroke and the second followed considerably later The first component of the split second sound begins just before the carotid incisura and represents aortic closure The tracings in this figure reflect part of the evidence indicating that in left bundle branch block, left ventricular ejection is delayed, and that in right bundle branch block left ventricular ejection does not tend to be delayed

The phenomenon of reduplication, although of no great clinical significance, is of considerable importance to the investigator of the mechanism of production of the first sound. Until we are able to explain the nature of reduplication, we cannot expect to advance far in our understanding of the first sound. There is good evidence to support the view that most single first sounds include the two major components which, when they are sufficiently separated in time, are responsible for reduplication. It has been observed from time to time for years that in bundle branch block, there is apt to be reduplication of the heart sounds.[14] This finding suggested the possibility that reduplication of sounds in such cases might be related to asynchronism in contraction of the two ventricles. As stated

above, Katz[11] had shown that in dogs, slight asynchronism in ejection from the two ventricles was a common occurrence. It therefore seemed possible that such might also be the case in humans and that this asynchronism might be considerable when bundle branch block is present.

An attempt to test this hypothesis by roentgenkymograms of aortic and pulmonic pulses timed by electrocardiograms showed that in left bundle branch block ejection into the aorta began several hundredths of a second after ejection into the pulmonary artery.[6] This delay in aortic ejection could be confirmed by simultaneous electrocardiogram and carotid artery tracing In such cases, both components of the sound preceded the carotid pulse. However, in certain ventricular extrasystoles interrupting left bundle branch block, carotid pulsation was found to occur earlier than during regular rhythm despite the smaller pulse and consequently slower transmission to the carotid (Fig. 4). In right bundle branch block, however, no delay in aortic or carotid pulse has been found (unpublished observations).* *Pulmonic artery pulsation*, in contrast to what was found in left bundle branch block, tended to lag behind aortic pulsation in cases with split first sounds. One component of sound tended to precede and one to follow the beginning of the carotid pulse. In cases with split first sounds and no bundle branch block, there was also found asynchronism in the beginning of ejection into the two great vessels.

These data seemed to favor the view that splitting of the first sound, at least in certain cases, was associated with asynchronism in the beginning of ejection from the two ventricles and that, in all probability, one component was produced in each ventricle. However, the evidence which we regarded as most important in favor of this view was of a different type. We have mentioned above the fact that the time relation of auricular and ventricular contraction may have a very important effect on the loudness of the first sound. This is reflected in sound tracings by variation in amplitude of recorded vibrations.

It seemed, therefore, that if cases could be found which showed constant splitting of the first heart sound and varying auriculoventricular relationships from beat to beat, it would be interesting to observe the behavior of each component of the first sound. We have had the opportunity to study two such cases in considerable detail.[15] In both cases, each component of the first sound was influenced by its own time relationship to auricular contraction (Fig. 5). Thus, in any given beat both components might be represented in the tracing by (1) large vibrations; (2) small vibrations; (3) the first component having large vibrations and the second small vibrations, or (4) the first component having small vibrations and the second large vibrations. It seemed to us that such behavior could not be accounted for if both components arose in a single ventricle, but on the other hand made necessary the hypothesis that one of the two major components arose in each ventricle.

* There is one exception to this statement In premature beats with a feeble pulse, the beginning of ejection may be greatly delayed without corresponding delay in the first heart sound (Unpublished observations)

Although the evidence mentioned above would appear to indicate that in split first sounds each ventricle contributes a component, the possibility cannot be denied at present that in certain cases splitting of the sound in one ventricle may occur. However, there is, as yet, no valid evidence to support such a view.

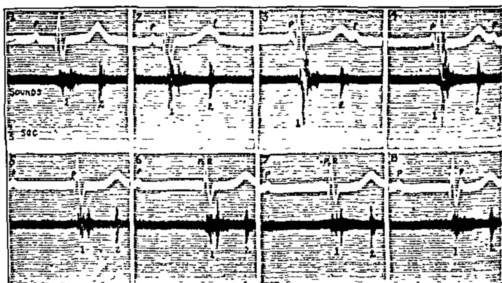


FIGURE 5 Complete heart block and split first heart sounds Beats were selected from a continuous strip of tracing to show the effect of varying As-Vs relations on each component of the split first sound Either component may be represented by small or large vibrations depending on its own time relation to auricular contraction

When the two major components of the first sound are clearly separated, it is noted that each is of extremely short duration, usually less than that ordinarily found in the first sound (Fig. 3). It is probable, therefore, that in single first sounds both components are usually present and partially superimposed. If the asynchronism is a little greater so that the two components are recorded side by side but not actually separated, the muffled or impure first sound results. However, in some cases there appears to be only a single component to the first sound. The clearest example is seen in certain cases of left bundle branch block which exhibit *a first sound, a pause* and then a systolic murmur, an auscultatory finding pointed out by King.[14] In such cases the sound in all probability emanates from the right ventricle. In cases without bundle branch block but with very short single first sounds—the type often described as valvular—one may venture to think that this quality is due to the fact that only one component is loud enough to be heard.

When we consider how the first sound is actually produced, it is clear that the dynamic factor must be ventricular contraction. Available evidence points to the view that the major vibrations occur during the isometric period of ventricular contraction and probably while intraventricular pressure is rising rapidly. This force sets up vibrations which

are quickly damped. What structure or structures are actually set into vibration in such fashion as to produce sound has not as yet been established. Some workers adhere to the view that the auriculoventricular valves are the important source of vibrations,[16] whereas some believe that various other structures are also concerned.[17] So far as we are aware the evidence available at present does not clearly establish either view. Furthermore, we no not know just what it is that governs the magnitude of the vibrations and therefore the loudness of the sound. It seems probable that the significant factor is the gradient of the rise of intraventricular pressure (the amount of force in terms of the speed of its development) in each ventricle and its effect on setting ventricular structures into vibration. Such an hypothesis, whether eventually proven to be valid or not, appears to account better than any other now available for the behavior of the first sound.

THE SECOND HEART SOUND

It may be regarded as established that the second heart sound is produced by after vibrations due to closure of the semilunar valves. This sound has two components, one furnished by aortic closure and the other by pulmonic closure. According to Wiggers,[3] the shortness of the sound is due to the quickness with which the vibrations are damped by the friction of the blood and lessening of their frequency as the pressure falls.

Wiggers[17] states that the intensity of the aortic and pulmonic second sounds varies roughly with the mean pressures in the respective circuits, but that dynamic studies show them to be more definitely related to the actual pressures existing in the large vessels at the very beginning of diastole. It is questionable whether or not Wiggers' view is adequate. It fails to explain the fact that extrasystoles and the more premature beats during auricular fibrillation sometimes have second sounds as loud as more effective beats (Fig. 1 *C* and 2 *B*). Furthermore, the fact that the pulmonic second sound may be quite as loud as the aortic, even though the pressure at the moment of closure must be very much lower, suggests that factors other than the actual level of pressure play an important part.

It would seem possible, therefore, that the difference in pressure in a ventricle and in its corresponding great vessel, which must govern the speed of closure of a semilunar valve, might be as important as the actual level of pressure in responsibility for the intensity of the sound. Thus, if the gradient of fall of intraventricular pressure were comparatively steep just prior to valve closure, movement of the valve toward the position of closure should be correspondingly rapid and the after vibrations correspondingly more intense and productive of a louder sound.

Clinicians have long taken into account another factor which must be concerned in the production of the second sound, *viz*, the physical state of the valve leaflets The character of the sound should depend not only on the speed and the pressure of closure, but also on the capacity of the valves to be set into vibration, analogous to the string or reed of

a musical instrument. This factor has received much attention in connection with the aortic second sound.

To how great an extent thickening or disease of the aortic leaflets modifies the aortic second sound is not known with certainty. The accentuation attributed to this factor may be due partly in some cases to a more anterior position of the ascending portion of a normal aorta or to dilatation, or tortuosity, and, consequently, better transmission of the second sound to the surface. Whatever may be the actual mechanism concerned in the change in sound, either an accentuation or a definitely higher pitch of the aortic second sound (in the absence of hypertension) should immediately lead to suspicion of thickening of the valve leaflets or disease of the aorta. On the other hand, marked diminution or absence of the aortic second sound, not accounted for by low blood pressure, should suggest lessened mobility of the valve and lead to a careful search for aortic stenosis or insufficiency

Arterial hypertension tends to cause increased loudness and higher pitch of the aortic second sound However, the enormous variability of the sounds in patients with similar degrees of hypertension is most impressive. Satisfactory explanations for these differences are not available but they may be due at least in part to factors discussed above.

The various diseases that are known to cause hypertension in the pulmonary arterial system, such as pulmonary arteriosclerosis, pulmonary emphysema, congenital defects with left to right shunt, and certain types of left-sided heart disease (particularly mitral stenosis), frequently have associated with them accentuation of the pulmonic second sound. The main change is usually in loudness of the sound rather than pitch and timbre; in this, it tends to differ from the aortic second sound. Before deciding whether the pulmonic second sound is altered from the normal, however, the examiner should always take into account the age of the patient as well as the thickness of the chest wall. In youth and in the thin-chested, the sound tends to be comparatively louder.

Splitting of the Second Heart Sound: Splitting or reduplication of the second sound is very common in both healthy and diseased hearts. Two so-called types have been described: That due to asynchronous closure of the aortic and pulmonic valves; and that due to asynchronous closure of leaflets of either valve. Whether or not the latter type occurs is doubtful; in most cases the reduplication is clearly due to asynchronism in closure of the two valves. It is present in many cases of bundle branch block[6] (Fig. 4 *C*) and of ventricular extrasystoles as well (Figs. 2 *B*, *D*, and *E*), unless the beat is highly premature and ineffective. It may be discovered in many cases with reduplication of the first sound, whether the heart is healthy or diseased. On the other hand, it occurs frequently when no splitting of the first sound is discoverable

There are at least two reasons why the second sound may be split when the first sound is not. In the first place, the components of the second heart sound are shorter in duration than those of the first; therefore, an equal grade of asynchronism might merely prolong the first sound without causing separation, whereas it might bring about clear-

cut separation in the second sound that could be both heard on auscultation and registered in sound tracings Secondly, the length of dynamic systole in the two ventricles may vary.[11] This is probably best exemplified in certain cases which, in different phases of respiration, show no change in the duration or frequency of the vibrations of the first sound, whereas the two components of the second sound may vary in position from superimposition to complete separation and reduplication (Fig. 6).

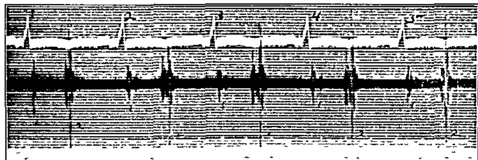


FIGURE 6 Phasic respiratory splitting of the second heart sound. In the first and fifth beats, the two components are approximated closely enough to give the impression of a prolonged second sound In beat three they are completely separated

The observations of Katz[11] indicate that these changes may de dependent on variations of blood inflow to the two sides of the heart during the different phases of respiration or to vagus effect.

THE MID-SYSTOLIC CLICK

In 1913, Gallavardin[18] described a clicklike sound which occurs during ventricular systole and falls between the first and second heart sounds In discussing this finding he applied two terms to it, namely "pseudo-reduplication of the second heart sound" and "telesystolic extracardiac sound." We have suggested the less cumbersome term of mid-systolic click.[19] The chief objection to this term is that the sound does not necessarily fall in mid-systole, but may occur earlier or later than this point Lian and Deparis[20] independently called the sound "Le Claquement meso-systolique pleuro-pericardiale," a term very similar to ours except for the last word which refers to Gallavardin's and their own conception of the mechanism of production of the sound Gallavardin stated that in three cases which had exhibited the sound during life, pleuropericardial adhesions were found at necropsy He believed, therefore, that the sound is produced by tugging on pleuropericardial adhesions during systole, a view which at this time cannot be regarded as established The clicklike sound can be imitated in the cadaver by moving the heart against a subpleural emphysematous bulla with the lung applied to the inner chest wall while one auscults over this area. Furthermore the sound is similar to that which can be produced by injecting air into the mediastinal tissues (unpublished observations).

The sound is a click or crepitating noise not at all like any sound known to be produced within the heart except the opening snap of mitral stenosis which it sometimes resembles in quality but not in time relations. It is usually a single sound but there may be two or even three sounds in rapid succession which may give the auditory impression of a short friction (Fig. 7). It is usually heard best near the apex but

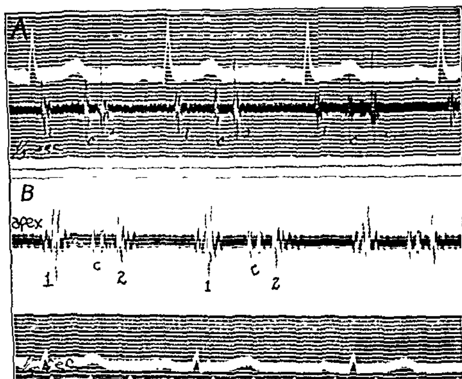


FIGURE 7 The mid-systolic click *A*, Variation in time relations to first and second heart sounds *B*. A double click.

occasionally as high as the third interspace. It is often loud enough to be heard over the entire precordium. Although it tends to fall about midway between the first and second sounds, it may be near enough to one or the other to be mistaken for reduplication by those who disregard its other qualities. In many cases, there is a phasic respiratory variation in its time relations to the first and second sounds, so that in one phase of respiration it may be nearer to the first sound and in another nearer to the second sound.

The mid-systolic click is quite common, although usually overlooked by those who are not familiar with its characteristics. So far as we have been able to ascertain, it has no pathological significance. It is usually found in healthy individuals but occasionally is present in patients with one or another type of heart disease. Its chief clinical importance is that it is sometimes wrongly interpreted and mistaken for evidence of heart disease. It is for this reason that all who examine hearts should be able to recognize it.

GALLOP RHYTHM AND THE THIRD HEART SOUND

The presystolic type of gallop or canter rhythm was clearly described as early as 1838 by Charcelay.[21] Potain,[22] however, has been the most important contributor to this subject. He divided gallop rhythm into three types; protodiastolic, mesodiastolic, and presystolic, and distinguished them from splitting of the first and second heart sounds. He

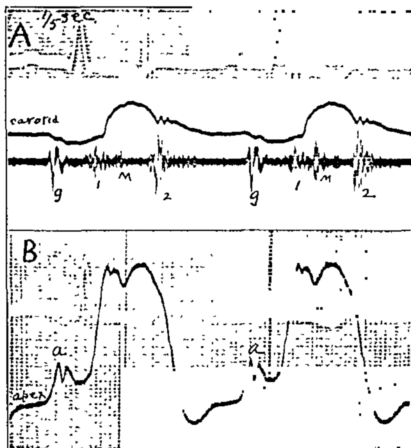


FIGURE 8. Presystolic gallop rhythm *A*, Electrocardiogram, carotid pulse and sounds at the apex The gallop sound is represented by vibrations of much lower frequency than the first sound, the systolic murmur or the second sound *B*, Electrocardiogram and apex cardiogram The summit of the prominent presystolic wave (*a*) occurs at the same time as the gallop sound

also stated that the gallop sound could be heard in twenty per cent of normal individuals. Potain's classification has been modified in two respects: (1) Following the work of Gibson[23] and of Thayer,[24] the protodiastolic sound heard in individuals with healthy hearts, most frequently in children and young adults, has been called the physiological third heart sound. There has been a tendency to remove this sound from the category of gallop rhythm, despite the fact that Thayer believed that protodiastolic gallop and third heart sounds were produced by analogous if not identical mechanisms. (2) Most recent writers have denied the

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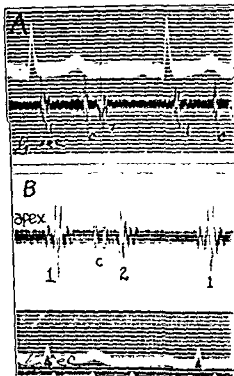


FIGURE 7 The mid-systolic click A, second heart sound



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considered are: (1) The so-called systolic gallop or other sounds which occur during systole; (2) reduplication of either the first or second sound, (3) the opening snap of mitral stenosis, and (4) the sound due to calcification of the pericardium The characteristics which differentiate them are noted in the appended table.

The presystolic gallop sound is clearly a result of auricular contraction, as was first stated by Charcelay. No dependable report of presystolic gallop in the absence of auricular beats is to be found in the literature. We have never recorded it when it was not in close association with the P wave of the electrocardiogram In nearly all cases it is initiated within a range of 0.08 to 0.14 second after the beginning of the P wave. If the sounds are recorded in conjunction with an apex cardiogram, it is found that the gallop sound falls at the peak of the wave produced at the apex by auricular contraction (Fig. 8). For these reasons we believe that the name might properly be changed from presystolic to auricular gallop, as has been suggested.[25] The time relations of the sound are determined solely by the position of auricular systole. It is usually "presystolic" because auricular systole usually falls shortly before ventricular systole. When auricular systole moves to some other position in the cardiac cycle, auriculosystolic gallop moves along with it. If the A-V interval is very short, the gallop sound may be so close to the first sound as to simulate splitting of the first sound (Fig. 9 *A*).

Protodiastolic gallop occurs within the range of approximately 0.12 to 0 20 second after the beginning of the second sound In quality and the areas of maximum intensity, the protodiastolic sounds are indistinguishable from presystolic gallop sounds. This sound falls at the summit of the wave of early diastolic ventricular filling. The statement has been made repeatedly in the literature that gallop rhythm does not occur in the presence of auricular fibrillation. This statement is true only so far as presystolic gallop sounds are concerned. Protodiastolic gallop rhythm occurs not infrequently in the presence of auricular fibrillation (Figs 10 and 12 *B*).

Summation Gallop Rhythm: It has long been known that gallop rhythm is most apt to be present when the heart rate is rapid, at least 100 beats per minute. Furthermore, it has been noted that prolonged auriculoventricular conduction time in some way favors the occurrence of gallop rhythm. Gubergritz[26] suggested that presystolic and protodiastolic sounds were due to similar mechanisms and in support of this view cited the observation that at various times the same patient might show one or the other type of gallop sound We have been able to confirm this observation by recording heart sounds, and we have also found that both types may be present at the same time (Fig 11 *A*). Furthermore, it has been possible to show that various forms of cardiac mechanism which tend to superimpose auricular contraction on the wave of early diastolic ventricular filling favor the production of gallop rhythm.[27] If either presystolic or protodiastolic gallop rhythm had previously been present, the coincidence of auricular contraction with early diastolic filling greatly increases the loudness of the sound (Figs. 11

and 12). If both protodiastolic and presystolic gallop sounds are present, increase in heart rate decreases the interval between them. If the rate goes above 100 they are apt to merge, with the production of a single sound much louder than would be expected from simple addition of the two sounds. In 1933 we presented evidence showing

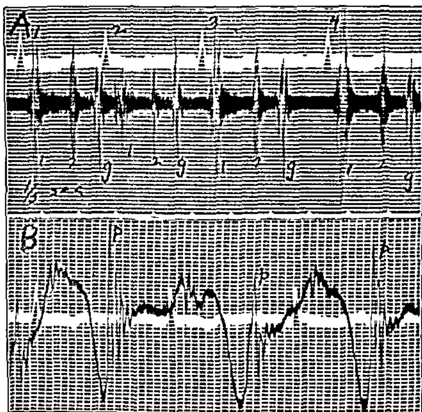


FIGURE 10 Protodiastolic gallop rhythm *A*, Loud gallop sounds in auricular fibrillation *The interval between the second and gallop sound (g) is less in beat two than in beat four* This variation is dependent on the duration of the preceding ventricular diastole *B*, Apex cardiogram, same patient The large protodiastolic wave (*p*) falls at the time the gallop sound is to be expected The time relations of the protodiastolic wave show the same variations as those of the gallop sound

the relationship between the behavior of gallop rhythm and the time relations of early diastolic and auriculosystolic ventricular filling.[27] The term "summation gallop" was used to refer to the gallop sounds either produced or intensified by coincidence of the two waves of ventricular filling. Further studies during the past six years have confirmed the validity and usefulness of the concept of summation gallop. This concept permits at least some understanding of what was formerly regarded as mysterious behavior. Most physicians, unless they are constantly on the lookout for faint, dull, low-pitched gallop sounds, rarely detect any type except summation gallop. Nearly all the loud gallop sounds which obtrude themselves on the ear are of this type. The criticisms which have been

offered against the hypothesis of summation[25] had all been covered by the evidence presented in the original paper and have therefore required no further consideration.

Clinical Characteristics: Potain has said that gallop sounds can sometimes be palpated better than heard. He was doubtless referring to

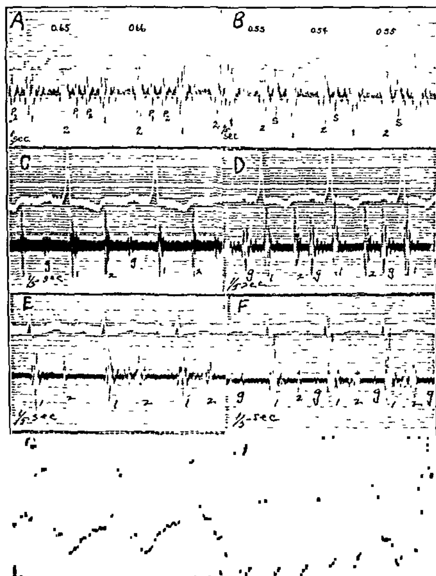


FIGURE 11 The effect of heart rate on gallop rhythm *A* and *B* from same patient In *A* both protodiastolic (*p*-1) and presystolic (*p*-2) gallop sounds are

its appearance and a diastolic wave (*p*) in the apex cardiogram (*H*) becomes prominent

the impact of the wave of ventricular filling which accompanies the gallop sound. To recognize gallop rhythm one must be familiar with the low pitch of the sound, the positions in the heart cycle it is apt

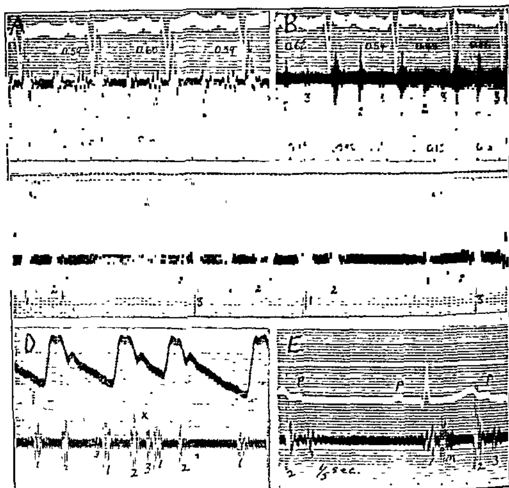


FIGURE 12 Effects of occurrence of auricular contraction in early ventricular diastole on the production of gallop sounds *A* and *B*, Same patient In *A* incomplete summation gallop rhythm is present producing a prolonged gallop sound (3) In *B* the rhythm has changed to auricular fibrillation so that only faint, much shorter protodiastolic gallop sounds (3) persist *C*, Incomplete heart block The gallop sound (3) is present only when the P wave occurs near the end of the T wave The most favorable position is just at the end of the T wave (beats two and five) *D*, In the premature beat, the P wave coming just at the end of the preceding ventricular systole causes a summation gallop sound (3). *E*, Two to one heart block The auricular beat falling before the ventricular beat causes only minor sound vibrations The auricular beat falling in early diastole causes a distinct gallop sound (3)

to occupy, the positions at which it is best heard (the apex or fourth interspace just to the left of the sternum) and the maneuvers which tend to accentuate it (such as placing the patient in the left lateral recumbent position, or employing some method to increase the heart rate).

Gallop sounds are very variable in their behavior. They are usually, but not always, best heard with the patient in the recumbent position

They may be present during one examination and absent at the next. They may even appear or disappear during a single application of the stethoscope if the rate changes (see Fig. 11). They tend to be more conspicuous during decompensation and may disappear with the recovery of compensation.

Gallop rhythm is usually "left-sided" and heard best at the apex, except in hypertensive disease with heart failure when it is frequently "right-sided" and heard best in the fourth interspace just to the left of the sternum. Apical gallop sounds are almost certainly produced in the left ventricle and those heard near the midline probably in the right ventricle.



FIGURE 13 The effect of respiration on third sounds In this case the third sounds (3) were loudest just at the end of expiration and faintest when the lungs were filled

Mechanism: The actual mechanism of production of gallop sounds has not been clearly demonstrated. Some workers believe that the additional sound is produced by vibrations set up in the auriculoventricular valves.[16] Others incline to the view that the wave of ventricular filling transmits an impact through the ventricular wall to adjacent structures such as the chest wall, setting them into vibration

Those who believe that gallop sounds are valvular in origin may be divided into two schools, namely, those who hold that the sounds are due to opening of the valves, and those who maintain that they are due to closure. The view that gallop sounds are due to opening of the auriculoventricular valves in diastole is easily ruled out by consideration of the time relationships, since the sound *falls* at the summit of the protodiastolic wave of ventricular filling which comes several hundredths of a second after opening of the valves. Those who believe the sounds are due to valve closure assume that waves of ventricular filling, by reflection back of the valves, push them to a position of closure, thus causing a sound. This hypothesis does not seem to us to be valid for the following reasons: (1) The sound comes at the summit of the wave of filling as recorded in the apex cardiogram (Figs. 10 and 11) and during the downstroke of the jugular V wave If it were due to valve closure, it should come after the summit of the filling wave; furthermore in right-sided gallop, if valve closure occurred at the instant of the gallop sound, there should be an interruption in the downward curve of the jugular tracing at the same instant, since the emptying of the venous

system would be checked if the A-V valves were closed. However, such is not the case. The downward curve may continue uninterruptedly for at least 0.02 or 0.03 second after the beginning of the gallop sound. (2) All sounds that we know to be valvular in origin are much higher in pitch and tend to be shorter in duration than gallop sounds.

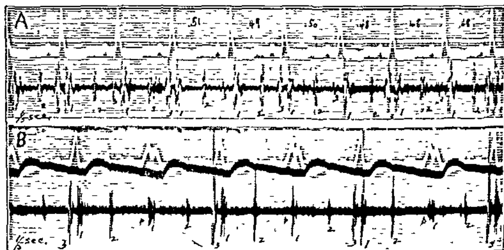


FIGURE 14 Alternation in gallop sounds *A*, True alternation in which the gallop sounds (3) were alternately quite loud and faint Although ventricular alternation was present, no definite alternation in loudness of either first or second sounds was detected *B*, Pseudo-alternation of gallop sounds (3) due to left bundle branch block in alternate beats The onset of left ventricular diastole is delayed when left bundle branch block is present so that the following auricular contraction occurs early enough in ventricular diastole to produce summation and, therefore, a loud gallop sound (*d*).

A wave of ventricular filling is indispensable for the production of gallop rhythm. Anything tending to increase the size or velocity of such a wave favors the production of a gallop sound. Among such factors are fever, anemia, hyperthyroidism or heart failure with increased intra-auricular pressure. In some cases, a third sound can be heard during only a part of the respiratory cycle (Fig. 13). Occasionally, alternation in the gallop sound is present (Fig. 14). Both of these phenomena are probably due to variations in the waves of ventricular filling. Other factors known to favor the production of gallop rhythm, aside from the summation phenomenon discussed previously, are such diverse conditions as acute rheumatic carditis, the so-called anterior or apical myocardial infarction, and the dilated, failing heart of hypertensive disease. It seems probable that in such conditions, the altered state of the heart muscle may offer less resistance to the impact of waves of ventricular filling. Available evidence suggests that in some cases the increased waves of filling are chiefly responsible for the production of the gallop sound; in others, myocardial change. However, the combination of these two factors is most apt to produce gallop rhythm.

The low pitch of the sounds, their areas of maximum intensity, their time relations to the waves of ventricular filling, the prominence

of these waves in apex cardiograms, their palpability when gallop rhythm is present, and the important bearing which the state of the ventricular muscle (but not the valves) has on the production of gallop sounds, would all seem to favor the "impact" hypothesis. The sound can be quite faithfully reproduced in the cadaver by gently tapping the finger against lung tissue applied to the inner chest wall and auscult-ing over the outside of the chest. It is a remarkable fact that gallop rhythm is not often heard with the patient in the upright position. However, in those cases in which it is heard in the upright position, it is apt to be much louder in the recumbent position. The most favorable position for eliciting gallop rhythm is usually the left lateral decubitus. It is not quite clear what bearing these facts have on the mechanism.

The conception of gallop rhythm presented above has a definite bearing on prognosis Thus, the larger the wave of filling or the greater its velocity, the less is the change necessary in the state of the heart muscle for the production of gallop rhythm. In hyperthyroidism with more rapid circulation time, and, because of tachycardia, only a single large wave of ventricular filling, it is quite probable that gallop rhythm (summation type) may occur with little alteration from the normal state of the heart muscle. On the other hand, as stated above, when the heart muscle is severely diseased there is good reason to believe that gallop rhythm may occur in spite of little change from the normal in the wave of filling. The prognosis, therefore, may be modified by various factors In such conditions as hyperthyroidism, anemia, or acute carditis, it is apt to be determined by the course of the underlying disease Thus, while gallop rhythm may still be interpreted as the cry of a heart for help,[29] the distress is not necessarily irremediable. Studies made in groups of cases showing gallop rhythm indicate that on the whole this disturbance has a serious prognostic significance. Such studies are of great value. Nevertheless, one must guard against the fallacy of venturing a prognosis in any patient on the basis of gallop rhythm alone, any more than on any other single finding. Gallop rhythm is a danger signal but one must still discover the nature and gravity of the danger.

The Physiological Third Heart Sound: This sound, which is very commonly present in healthy children and not infrequently in young adults, has auscultatory characteristics identical with gallop sounds. Over the chest wall, the sound heard is nearly always protodiastolic. Low frequency vibrations may sometimes be recorded during the presystolic period, but are only rarely audible[30] However, as long ago as 1914, Benjamins[30a] and more recently Taquini[30b] have recorded vibrations corresponding in time to auricular contraction when output receivers were placed in the esophagus at the auricular level. It would be difficult to determine to what extent these vibrations may be adventitious due to movements of the auricles against the output receiver. Such a finding does not permit the assumption that a sound is being produced within the auricles. For example, gently tapping the diaphragm of a stethoscope produces a sound which seems quite loud as one listens through the ear pieces; the cause of such a sound, however, is not movement of the finger

per se but its impact against an interposed structure capable of being set into vibration.*

The phenomenon of summation affects the physiological third heart sound as it does gallop rhythm. There are, however, important differences. In gallop rhythm there is usually good reason for believing that

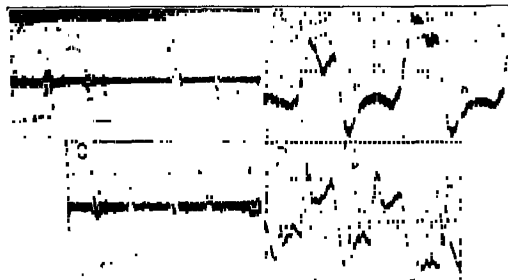


FIGURE 15 The physiological third heart sound *A* and *B*, Same patient *C* and *D*, Same patient In each case there is a prominent protodiastolic wave (*p*) in the apex cardiogram at the instant the third heart sound (3) occurs

waves of ventricular filling are increased in velocity or size, or that there is some disease of the heart muscle. In the healthy young people with physiological third heart sounds, there is no reason for believing any of these factors to be present. If, therefore, the sounds have a similar mechanism, it is necessary to postulate that in youth the heart muscle possesses some quality that later tends to be lost. Such a quality might be a certain pliability or elasticity, which would permit the impact of the wave of ventricular filling to be transmitted through the ventricular wall more readily than occurs in older, less elastic muscle. We have no proof to offer for such a view except for the fact that in apex cardiograms, rather large waves are found, corresponding in time to the third sounds, just as in the case of gallop rhythm (Fig. 15). If this view is correct, the mechanisms of the physiological third heart sound is closely related

* This factor may have considerable importance even when sounds are heard or recorded from the surface of the chest, provided impact is transmitted through the chest wall at that instant There can be little doubt that impact against the inner chest wall contributes to various sounds heard through the stethoscope or recorded These may be regarded for practical purposes as component parts of a heart sound although the actual place of origin of the vibrations is outside the heart. However, vibrations set up in an output receiver, because of the transmission of an impact through the chest wall (vibrations which would not be present except for the interposed output receiver), should not be regarded as a legitimate part of heart sounds but should be looked upon as an imperfection in technic

to that of gallop rhythm. The question may be asked why it is that, when the rate is slow enough to avoid summation, presystolic physiological third heart sounds are so much less frequently heard than presystolic gallop sounds. This may be due to the fact that in the young healthy heart, with no tendency to increased venous pressure, the auricle is not likely to contain a large amount of blood in the latter part of ventricular diastole, when auricular systole occurs, so that a large wave of ventricular filling would not be expected at that time.

THE PROTODIASTOLIC SOUND ASSOCIATED WITH CALCIFICATION OF THE PERICARDIUM

In 1933, Lian, Marchal and Pautrat[31] described a "strong vibrating" sound heard in early diastole in two patients with calcification of the pericardium. They termed it protodiastolic pericardiac vibration. We have observed and recorded this sound in several patients. The time relations of the sound are identical with those of protodiastolic gallop rhythm although the sound tends to be much sharper, higher-pitched, and louder. It has associated with it a vigorous apex impulse which falls at the same instant as the sound (Fig. 16). The mechanisms of the sound production is probably somewhat similar to that of gallop rhythm, with the sheet of calcium influencing the production of sound vibrations in some way as yet not understood. We have noted the loud sound only in cases with circumscribed calcified areas. In one case in which the heart was found to be almost completely encased in calcium, a faint sound with similar time relations could be heard only near the base. The extent of the area over which the sound is audible appears to depend on its loudness.

SYSTOLIC GALLOP RHYTHM

The term meso-systolic gallop was first proposed by Cuffer and Barbillon[32] who have received credit for the discovery of systolic gallop rhythm. However, the descriptions to be found in their article are vague and give the impression that they were mistaking such common conditions as splitting of sounds and diastolic types of gallop rhythm for systolic gallop. However, Potain[33] a little later clearly described the aortic type of systolic gallop rhythm. There has been, more recently, a tendency to include the mid-systolic click, with the systolic gallop sound.[34,35] The aortic systolic gallop sound falls about midway between the first and second sound. There is remarkable constancy in its time relations from beat to beat It is a little higher in pitch than diastolic gallop sounds but has none of the clicking or crepitating character of the mid-systolic click. It is heard best in the aortic area. It may occur in cases with typhoid or typhoidlike fevers (we observed it in one girl with acute miliary tuberculosis), hypertensive cardiovascular disease and aortic insufficiency. The last four cases in which we have discovered systolic gallop rhythm all had aortic insufficiency and it apparently occurs more commonly in this condition than any other. We were able to obtain a roentgenkymogram of the ascending aorta in one patient with aortic

regurgitation and systolic gallop rhythm.[36] It was found that the systolic gallop sound was synchronous with the peak of the systolic expansion of the aorta. It is probable that the sound is due to checking of the expansion of the ascending aorta (as was first suggested by Potain) or to the impact of the expanding aorta against surrounding structures.

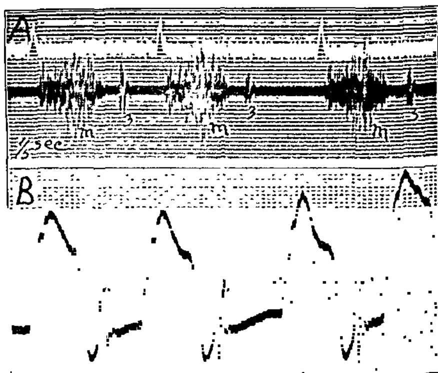


FIGURE 16. The protodiastolic pericardiac vibration. *A* and *B*, Same patient. There was a loud systolic murmur (*m*), a sharp third sound (3) and at the same time a sharp outward thrust at the apex (*p*)

A similar sound, heard at the apex in one of our cases with aortic systolic gallop rhythm[36] fell 0.04 second later than the aortic sound and was synchronous with the peak of a positive wave in the apex cardiogram, suggesting that impact of the ventricle against the chest wall as a factor in its production (Fig. 17). We have not as yet observed systolic gallop rhythm in any patient with a normal cardiovascular system.

THE OPENING SNAP OF MITRAL STENOSIS

This sound has been confused by some writers with reduplication of the second sound and by others with gallop rhythm. Duroziez,[37] Guttman,[38] Sansom,[39] and Rouches[40] described it and differentiated it from other heart sounds. It is a short, sharp, snapping or clicking sound, usually occurring 0.07 to 0.13 second after the beginning of the second sound. It is usually heard best in the third or fourth interspace, near the anatomical position of the mitral valve, this position being higher and farther to the right than the usual point of maximum intensity of left-

sided gallop sounds. We have made studies of its time relationships to various other cardiac events.[41] It occurs just before the beginning of the diastolic murmur of mitral stenosis (Fig. 18). In contradistinction to

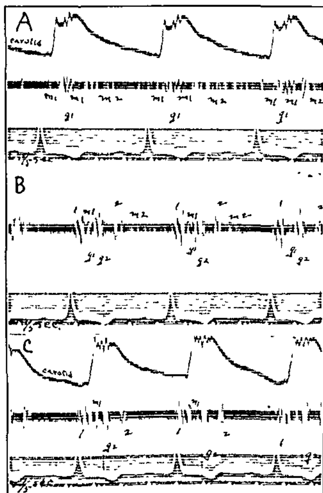


FIGURE 17 Systolic gallop rhythm *A*, *B*, and *C* from same patient In *A* the sounds were recorded in the first interspace to the right of the sternum At this position the only conspicuous sound aside from systolic and diastolic murmurs was a loud nearly mid-systolic sound (*g*-1) In *C* at the apex, first and second sounds were recorded and also a loud sound (*g*-2) slightly later in time than the mid-systolic sound recorded at the base In *B*, sounds recorded in the fourth interspace just to the left of the sternum show both the aortic and apical systolic gallop sounds (*g*-1 and *g*-2), split first and second sounds as well as the systolic (*m*-1) and diastolic (*m*-2) murmurs

the gallop sound, it does not have associated with it a prominent wave in the apex cardiogram, but occurs approximately 0.03 second before the small protodiastolic wave usually present in mitral stenosis. The significant time relationship of the snap in cases having split second sounds is with the aortic component (Fig. 18 *C*). The interval varies in auricular fibrillation, being shorter after highly premature beats and longer after

delayed beats. All available evidence indicates that the sound is due, as both Guttman and Rouches believed, to sudden curtailment of the opening movement of the stenosed mitral valve as the blood flow from the auricle to the ventricle begins in early diastole.

The opening snap has a practical value in the diagnosis of mitral stenosis second only to that of the characteristic murmur. It is present

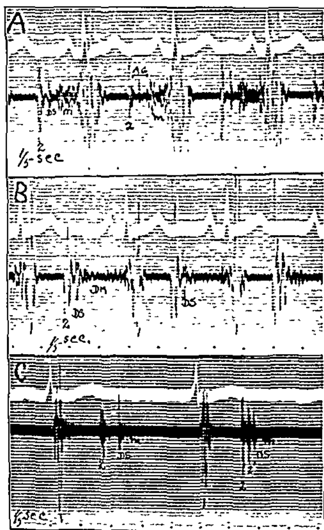


FIGURE 18 The opening snap of mitral stenosis. *A* and *B*, Same patient. *A*, Sounds were recorded where the diminuendo and crescendo murmur (*m*) of mitral stenosis was loudest in order to show its time relation to the opening snap (*DS*). The snap occurs during the auscultatory gap (*AG*) between the second sound and the beginning of the murmur. *B*, The sounds were recorded where the snap (*DS*) was loudest. At this area the murmur was relatively insignificant. *C*, Loud opening snap (*DS*) in a patient with mitral stenosis in whom the diastolic murmur (*m*) was barely audible In the second beat, the second sound is split (2, 2′) so that three separate loud sounds are heard in rapid succession The first of these represents aortic closure and it is to this sound that the snap (*DS*) maintains its significant time relation. In auricular fibrillation this time varies depending on the length of the preceding ventricular diastole.

in well over half the cases, and, in many, it is distinct and easily heard when the murmur is difficult to elicit. Its sharp, snapping, or clicking quality distinguishes it from all other sounds heard during diastole. Its point of maximum intensity and time relation to the second sound also help to differentiate it from both reduplication of the second sound and protodiastolic gallop rhythm. So far as our experience goes, the opening

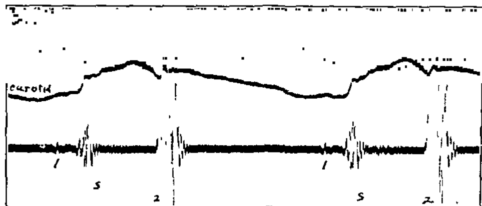


FIGURE 19. The semilunar opening click (s) recorded at the base At this area the first sound (1) was insignificant. The click was loud and sharp and preceded the carotid upstroke by 0 02 second The film was run rapidly to display time relations Each vertical line represents 0 01 second

snap occurs only in mitral stenosis. Others have stated that it occurs in aortic insufficiency and adhesive pericarditis. It may be heard in cases of aortic insufficiency in which mitral stenosis is also present, but not otherwise. The statement that it occurs in adhesive pericarditis is an error possibly due to confusing the opening snap with the "protodiastolic pericardiac vibration" of Lian, present in some cases with calcified pericardium. The two can be differentiated by the time relations and areas of maximum audibility of the sounds as well as by the fact that the pericardiac vibration has a sharp palpable impulse associated with it

THE SEMILUNAR OPENING CLICK

We have recently become aware of a sound occurring in early systole which we believe we had previously either overlooked or mistaken for the second component of a split first sound The characteristics of this sound are so distinctive that once they are known the sound is easy to recognize. The term semilunar opening click was adopted to call attention to the character of the sound, the area over which it is heard best and its time relations. It is loudest at the base either over the aortic or pulmonic area. When it occurs over the aortic area it can be shown by simultaneously recorded sound and carotid artery tracings, to fall within the range of 0.01 to 0.02 second before the primary carotid oscillation (Fig. 19). This means that it is approximately synchronous with the beginning of ejection into the aorta. When the sound is

heard best over the pulmonic area, the relations to the carotid pulse are not quite so constant, but it is probable that in such cases the sound is synchronous with beginning ejection into the pulmonary artery. The sound is short, high-pitched, and usually clicklike in character. The time of its occurrence is such that, grouped with a single first sound, the two may resemble a split first sound. However, the click may be present when the first sound is split. Under these circumstances the click in some cases may fall between the two components of the split first sound or in others may follow the second component.

The semilunar opening click is most likely to be found when the heart has extra work to do. Most of our patients in whom this sound was heard over the aortic area had systemic arterial hypertension. In two, aortic aneurysm was present. In the patients in whom it was heard best over the pulmonary artery, there was dilatation of the pulmonary vessels suggesting pulmonary hypertension. We have heard the sound in several patients with patent ductus arteriosus.

SOUNDS IN WHOSE PRODUCTION THE PRESENCE OF AIR PLAYS A PART

Water-wheel Murmur: The best known of this group of sounds is a spectacular churning or splashing noise, the so-called water-wheel murmur (bruit de la roue hydraulique) or bruit de moulin, heard over the precordial area when both fluid and air are present in the pericardial sac. These sounds may be very loud so that they are audible some distance from the chest; more often, however, they can be heard only by applying the stethoscope or ear to the precordial area. The sounds are rarely observed except in dealing with war wounds involving the chest. However, the combination of air and fluid in the left chest also has been described as producing a splashing sound. The presence of air and fluid in the pericardial sac does not necessarily mean that the water-wheel murmur will always be present. One of us failed to elicit it in a case in which approximately half of a large pericardial effusion was withdrawn and replaced by air.

Splashing Sound: Apparently the combination of a large overactive heart and just the proper mixture of gas and fluid in the stomach may also produce a splashing sound with each heartbeat. O. H. Perry Pepper[42] has reported such a case and refers to a similar case previously reported by Spillman and Perrin[43] While making rounds, he heard a similar sound in a patient with aortic insufficiency and a very large heart. The splashing sound in this patient lasted for only a short time and was not heard again during his stay in the hospital. This sound has little clinical significance beyond the fact that it should not be confused with the water-wheel pericardial murmur.

The Pericardial Knock: This designation has been applied to a knocking or tapping sound heard over the chest usually during the systolic phase of the heartbeat, in certain cases with left-sided pneumothorax. The term seems inept, since, so far as is known, the pericardium is not an important factor in the production of the sound. According

to Barnwell,[44] it was first suggested because of the finding of a shell fragment in the pericardium of a patient exhibiting the sound. This is also one of the sounds which may be quite loud and heard some distance from the chest. The patient is usually quite aware of its presence. Scattered case reports are to be found in the older literature. Rees and Hughes[45] reported nine cases with very loud tapping sounds following war wounds of the chest, although some of their cases may not have

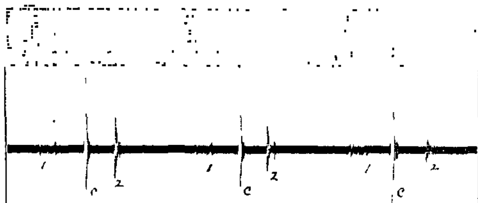


FIGURE 20 Mid-systolic short loud crepitating sound (c) in a patient with mediastinal emphysema

belonged in this group. Various explanations for its mechanism have been offered. Barnwell and Greene[44] suggested two possible mechanisms (1) the free diastolic fling of the heart against the left diaphragm over a distended hollow abdominal viscus, (2) the uncushioned systolic impact of the heart against the chest wall in cases of left pneumothorax. Cooper (observations to be reported) has found that the sound can be elicited in a large proportion of patients in whom left-sided pneumothorax has been induced in the treatment of tuberculosis He observed, however, that it was necessary to place the patients in certain positions of recumbency, usually in the left lateral decubitus, in order to produce the sound. It is tremendously influenced by the phase of respiration. In studies of some of these patients made with Cooper, we concluded that impact against the chest wall of the partially collapsed lung, as it is moved with the heart during systole, is responsible for the sound. The lung movement *can easily be seen by fluoroscopy Furthermore, this hypothesis fits in* well with the influence of position and respiration on the production of the sound.

Sounds Due to Mediastinal Emphysema: The most important discussion of this subject is found in the recent paper by Hamman.[46] It was Hamman's belief that in his cases there was interstitial emphysema of the lungs which traveled to the mediastinum Presumably the cause of the sound is movement of the heart against the emphysematous tissue, with the production of sounds analogous to those produced by the pressure of a stethoscope against subcutaneous emphysema. These

sounds may be quite loud. They are noted by the patient himself and may sometimes be heard across the room. Hamman used many adjectives in describing the sound, including such terms as crunching, crackling, crepitating, bubbling, clicking and popping. We have observed a similar sound in one patient after perirenal air injection and in another after paravertebral novocain injection of the upper thoracic sympathetics. In both patients a loud crackling sound was heard during systole (Fig. 20), but one case differed from those of Hamman in that at times a similar but less loud sound could be heard during diastole. We assumed that in our cases, air had traveled to the mediastinal space from the sites of injection. In one, air could be demonstrated in the mediastinum by roentgenogram. Mencher,[47] has shown that mediastinal emphysema is not uncommon after perirenal air injection. So far as we are aware, this sound has not been observed previously after paravertebral injection. We have been able to duplicate the sound heard in our patients by injecting air into the mediastinal tissues of a dog.

SOUNDS ASSOCIATED WITH AURICULAR CONTRACTION

There are certain sounds due to auricular activity such as auricular friction sounds (observed occasionally in pericarditis) and murmurs (commonest in mitral stenosis) which do not fall within the scope of this discussion We have discussed previously two effects of auricular contraction on sounds emanating from the ventricles. These are the influence of the As-Vs time relation on the loudness of the first heart sound and the role played by auricular contraction on the production of presystolic and summation types of gallop rhythm.

It has long been known that sounds corresponding in time to auricular activity can often be heard in cases of heart block. As long ago as 1897 Pouzin[48] supported the view that these sounds were due to closure of the auriculoventricular valves following immediately after auricular contraction.* Gallavardin[49] dissented from Pouzin's view and held that these sounds are analogous to those of gallop rhythm and arise in the ventricles. He proposed that the auscultatory sign be called "galop du block."

Lewis,[51] on the basis of phonocardiographic studies, found that there is sometimes a "double auricular sound." He suggested that the first is due to contraction of the auricles and tension in its walls and the second due to closure of the auriculoventricular valves following cessation of flow from auricules to ventricles. When only a single sound is heard, Lewis

*Griffith,[50] in studying a case of this type, made the further observation that when auricles and ventricles contracted at about the same time, the first heart sound was likely to be much louder than in other beats Griffith's observation, apparently not considered important at that time, led eventually to the discovery that the time relations of auricular and ventricular activity exert a powerful influence on the loudness of the first sound even when the cardiac mechanism is normal, a phenomenon which we have discussed in connection with the first heart sound. However, it is clear that the contribution of the auricles to the production of the first heart sound is indirect, due to the effect of auricular discharge on ventricular activity, and not due to sound originating within the auricles themselves

suggested that it is due to valve closure. In our experience the double auricular sound is extremely rare. We have recorded it in only one case. It is possible that the second component of the sound is due to auriculo-ventricular valve closure. In both Lewis' case and our own, it began

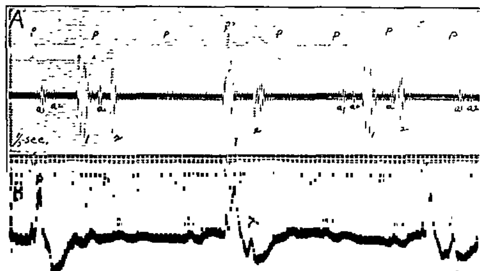


FIGURE 21. *A*, "Double auricular sound" (*a*-1, *a*-2) in complete heart block When auricular contraction falls during ventricular contraction, an extra sound (*a*) is recorded having the same time relation to the P wave as the first component (*a*-1) of the "double sound" *B*, Apex cardiogram. Same patient (The P waves in the electrocardiogram can barely be seen due to failure to loosen and standardize the string) When, however, the auricles beat during certain phases of ventricular systole, an extra wave (*x*) may be seen in the apex cardiogram much larger than waves caused by auricular contraction during ventricular diastole (*a*). We interpret these large waves as indicating that auricular contraction was moving the ventricle as a whole against the chest wall During diastole when the ventricular wall is flaccid no such wave is found, but only small waves of filling.

approximately 0.30 second after the beginning of the P wave (Fig 21). However, we have not observed this late sound in the presence of normal rhythm,* although we have recorded it as a single "auricular sound" in cases of heart block.

The first component is apt to fall 0 08 to 0.14 second after the beginning of the P wave, as is the case in presystolic gallop rhythm It is probably not due to A-V valve closure We have pointed out previously in this discussion that presystolic gallop sounds precede that event. In both Lewis' and our case of heart block a sound, having the same time relation to auricular activity as this first component, was heard and recorded even during the ejection period of ventricular systole (Fig. 21).

Characteristics of the so-called auricular sound, which falls in the range of 0 08 to 0.14 second after the beginning of the P wave in cases

* If due to A-V valve closure, it could not occur when the P-R interval is normal, since the valve would already be closed by ventricular contraction

TABLE 1

Extra Sounds Associated with the Heartbeat and Some of Their Characteristics

	Point of Maximum Intensity	*Time Relation*	*Character*	*Remarks*
Reduplicated first sound.	Apex or just to left of lower part of sternum.	Interval 0 04 to 0 12 second	Both sounds similar altho one may be louder than the other	Easily differentiated by the time relations from all extra sounds except late presystolic gallop and semi-lunar opening click Common in both healthy and diseased hearts
Semi-lunar opening click.	Aortic or pulmonic area	Synchronous with beginning of ventricular ejection	Sharp, clicking or snapping	Differentiated from reduplication of the first sound by area of maximum intensity Rare
Mid-systolic click	Inside apex fourth or fifth interspace	Between first and second sound Often varies with respiratory phases.	Sharp snap or clicking sound	No clinical importance Must be differentiated from apical systolic gallop rhythm Fairly common No pathological significance
Systolic gallop	Aortic area or apex	Constant and about midway between the first and second sound	Medium pitch. May be loud or faint	The aortic type is distinctive The apical type must be differentiated from the mid-systolic click. Rare
"Pericardial knock."	At apex or to left of heart	Inconstant Usually systolic but may also have diastolic component	Knocking May be very loud	Occurs in cases with air in left pleura space Can often be elicited after left-sided pneumothorax.
Sounds due to mediastinal emphysema.	Precordial area	Usually systolic. May have diastolic component.	Snapping or crunching May be very loud.	May follow spontaneous pneumothorax or perirenal air injection Resembles the pericardial knock Rare
Sounds due to agitation of air and fluid in stomach by the heartbeat.	Lower precordium and epigastrium	Systolic and diastolic.	Splashing sounds	Appears to require for its production large overactive heart as well as the appropriate combination of air and fluid in the stomach Extremely rare.
Reduplicated second sound.	Base.	Interval 0 03 to 0.11 second	Both sounds usually have similar character, altho one may be louder or higher pitched than the other.	Must be differentiated from the opening snap Common in both healthy and diseased hearts.

TABLE 1 (Continued)

Extra Sounds Associated with the Heartbeat and Some of Their Characteristics

	Point of Maximum Intensity	*Time Relation*	*Character*	*Remarks*
The opening snap	Just below mitral ring third or fourth interspace	0.07 to 0.13 second after second sound	Sharp snap or clicking sound Loud or faint	Must be differentiated from reduplication of the second sound Common in mitral stenosis and pathognomonic of this lesion.
"Physiological" third heart sound	Inside apex, usually fourth interspace	0.12 to 0.18 second after second sound.	Usually faint, low-pitched	Cannot be distinguished from gallop except by absence of heart disease Common in youth
Protodiastolic gallop	Inside apex, usually fourth or fifth interspace	0.12 to 0.20 second after second sound	Usually faint, low-pitched	Cannot be distinguished from physiological third heart sound except by presence of heart disease Common in diseased or failing hearts
Presystolic (auricular systolic) gallop	Inside apex, usually fourth or fifth interspace	0.08 to 0.14 second after beginning of P.	Usually faint, low-pitched	Ability to time it before the first sound is most important differential point. Common in diseased or failing hearts
Summation form of gallop	Inside apex, usually fourth or fifth interspace, or just to left of sternum	Usually 0.12 to 0.20 second after second sound	Low-pitched, may be faint, loud or short murmur	The rate usually exceeds 100 beats per minute unless delayed conduction is present Occurs when auricular systole falls close to preceding ventricular beat. Common in diseased or failing hearts
Protodiastolic pericardiac vibration	Precordial	Usually 0.12 to 0.20 second after second sound.	*Strong vibrating sound*	*Louder than normal heart sounds* *Differentiated from* protodiastolic gallop and physiological third heart sound by its constancy and greater strength, from the opening snap by greater intensity and longer interval after the second sound. Pathognomonic of pericardial calcification
"Auricular Sounds" Early Type	Apex.	0.08 to 0.14 second after beginning of P wave	Low-pitched	Heard in heart block Similar to presystolic gallop
Late Type	Third or fourth interspace	0.24 to 0.30 second after beginning of P wave	Low-pitched	Heard in heart block Mechanism not known

of heart block, are as follows: (1) It is likely to be much louder when it is superimposed on early ventricular filling than at any other time (in this respect behaving like summation gallop). (2) It is low-pitched. (3) It is heard best near the apex. All these findings, together with its time relations, support Gallavardin's view that it is a form of gallop rhythm and that, although the sound results from auricular activity, it actually arises in the ventricle. Such an explanation, however, does not account for the sound heard during ventricular systole. In our case this sound, like the first component during diastole, was also heard best at the apex. An apex cardiogram and a roentgenkymogram of the left ventricular border both showed a wave whose peak was simultaneous with the sound. In the former, the auricular wave during ventricular systole was very prominent (Fig. 21 *B*). We concluded, therefore, that auricular systole, occurring during ventricular systole, pushed the contracting ventricle against the chest wall causing impact and producing sound.

One may raise the question as to why "*galop du block*" should be relatively commoner in cases of heart block than is presystolic gallop rhythm in cases with a normal cardiac mechanism. We have been much impressed by the rapidity and extent of ventricular dilatation which may develop when complete heart block replaces normal sinus rhythm. One possible mechanism is that, under such circumstances, the thickness of the ventricular wall must be decreased so that a wave of ventricular filling caused by auricular systole would result in less absorption of the impact in the ventricular wall (and therefore more transmission to the chest) than would be the case if that wall were thicker. Furthermore, in cases of heart block with slow ventricular rate, ventricular systole is prolonged so that in early diastole the auricles are likely to be engorged with blood. If auricular contraction comes at such a time it is apt to augment greatly the wave of the early diastolic filling, a circumstance which would be favorable to the production of sound.

In some cases of heart block, a sound associated with auricular activity is heard best in the third or fourth interspaces and not at the apex. So far as we are aware, these sounds have not been carefully studied but they may be the same as the second component of the double auricular sound. Their position suggests that they might be due to A-V valve closure. It seems to us unlikely that they are due directly to contraction and tension of the auricular walls but this possibility has not been excluded.

The problem of "auricular sounds" needs further study, particularly in cases of complete heart block. On the basis of evidence available at present, it is clear that at least two and probably three different mechanisms may produce so-called auricular sounds. The earlier of the two auricular sounds which may be heard during ventricular diastolic periods in heart block resembles presystolic gallop sounds so closely that it, like presystolic gallop, is almost certainly caused by the effect of auricular contraction on the wave of ventricular filling. The later "auricular sound" which has been observed only in cases of heart block may be due

to auriculoventricular valve closure. The auricular sound noted during ventricular systole cannot be due to either of these mechanisms. The limited observations made suggest that it is due to the effect of auricular contraction in pushing the contracting ventricle against the chest wall. The question as to whether auricular contraction and tension of its walls produces sound which can be heard by the stethoscope remains open.

Table 1 points out characteristics tending to differentiate these extra or additional sounds.

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5A

Historical Origin and Evolution of Certain Congenital Anomalies of the Heart and Great Vessels

The tremendous progress that has been achieved in the last two decades in the surgical treatment of certain congenital anomalies of the heart and great vessels warrants a consideration of the historical aspects of the subject. *At the present time nearly one hundred congenital anomalies of* the cardiovascular system have been described. Only a few of them will be considered in this discussion

The medical pioneers who so well established the basis for the recent progress in this field comprise clinicians, physiologists, pathologists, anatomists, embryologists and surgeons.

For nearly fourteen and a half centuries little or no progress was evident in the field of the cardiovascular system following Galen's (138-201 A.D.) incorrect concept and teachings[27] Galen completely lacked the concept of the circulation of the blood and was led into serious error by attempting to merge purely speculative physiologic hypotheses of convenience with inaccurate and incomplete anatomic observations. It was with fanatical zeal that his followers unequivocally accepted his fallacious concepts. As late as 1649, Jean Riolan (Riolanus) (1577-1657) is credited with the statement that if subsequent dissections and observations differed from those of the Master (Galen), any discrepancies were attributable to the fact that nature had changed.[27]

It was not until 1628, when William Harvey's correct exposition of the circulation of the blood appeared, that constructive progress in the field of the cardiovascular system occurred. In his monumental work, *Exercitatio anatomica de motu cordis et sanguinis in animalibus*, Harvey also described the fetal circulation and the flow of blood through the foramen ovale (functional two-chambered heart). He wrote:

"Thus in embryos, while the lungs are yet at rest and have no action or motion, as if they were not present, nature makes use of the two ventricles of the heart as one for transmission of the blood

"In this and like vagaries of the embryonal cardiovascular development which perforce must be called normal lie opportunities for a multiplicity of congenital anomalies of the heart and great vessels which do in fact heavily afflict deplorable members of each generation born."[14]

PATENT DUCTUS ARTERIOSUS

The usual reference to the ductus arteriosus as the "ductus botalli" represents an eponymic error. Castiglioni has discussed the historical mystery of one Botallo who is believed to have confused the foramen ovale with the ductus.[7] So many contradictory statements concerning Botallo are recorded that it has been impossible to solve the enigma of his identity, to say nothing of his contributions. One page of history states that he was born in 1530, the same year that other references indicate as the year of his graduation, and he is said also to have been a student of the famous surgeon, Lanfranc, who lived more than two centuries earlier.[7]

The first authentic record concerning the discovery of the ductus arteriosus is the observation of Giulio Cesare Aranzio (1530-1589), Professor of Anatomy at Bologna,[7] who extensively studied the anatomy of the fetus and made his observations about the middle of the sixteenth century.

In 1593, Giambattista Carcano (1536-1606) of Milan, Professor of Anatomy at Pavia, confirmed Aranzio's findings when he also described the ductus arteriosus.[7]

According to Peacock, in 1757 Reimann recorded an instance of patent ductus arteriosus in an infant in whom postmortem examination revealed the left subclavian artery issuing from the ductus.[22] Reimann's report, a work of German origin, is the first published record of this compounded anomaly.

Numerous other references found in the early literature are chiefly concerned with the revelation of patency of the ductus arteriosus as disclosed at postmortem examination. In 1836, Lediberder of France described an instance of the type in which the ductus is merely a fistulous communication between the aorta and the pulmonary artery.[16]

In 1845, Norman Chevers (1818-1886) of London made the first report of typical solitary patency of the ductus arteriosus occurring in an adult.[9] Postmortem examination verified the clinical diagnosis. As early as 1847, Babington, of England, observed vegetations involving the patent ductus and was the first to record the complication, which is now known as subacute bacterial endarteritis.[3]

The characteristic murmur of patency of the ductus arteriosus is at times referred to as "Gibson's murmur." George A. Gibson (1854-1913) of Edinburgh was the first to emphasize and describe the characteristic murmur as a diagnostic sign of the anomaly. He stated:

> "The most characteristic physical sign is a murmur in the second left intercostal space over the septum where the thrill is felt, and this murmur is of late systolic rhythm, that is to say, that when compared with the apex beat it distinctly follows it. The murmur is usually somewhat long in its duration, and of a high-pitched character; it is usually louder on deep inspiration. It is further frequently accompanied by considerable accentuation of the pulmonary second sound, due to the increase of pressure in the pulmonary artery."[12]

Because of the fact that patency of the ductus arteriosus was the first congenital anomaly of the heart to be treated surgically, it is of unusual interest to recall the prophetic publication of John C. Munro (1858-1910),

a surgeon of Boston, Massachusetts, who in 1907 predicted the feasibility of surgical closure of the patent ductus. Munro expressed his prediction as follows:

". . . After death, which took place without oedema or marked cyanosis, [illegible] sections, and satisfied myself that it would be possible to ligate the duct provided a diagnosis could be made beforehand. . The operation I would propose, as demonstrated on the cadaver, is as follows: Under ether, which I prefer to chloroform in any case involving collapse of the lung, the sternum can be easily split along its centre or a little to the right, opposite the second costal cartilage. This is easily done with knife The sternal halves are then retracted, ample room for working being obtained. The right pleural cavity will probably be opened but the left one will not. Judging from analogous cases in surgery, this should not be serious, but if necessary the physiologist's apparatus for maintaining artificial respiration could be employed. I hardly believe that it would be needed After retracting the thymus upward, the pericardium is exposed Its reflection lies so high on the large vessels that the ductus to all intents and purposes is intrapericardial In the upper angle the aorta will be seen on the patient's right and the pulmonary artery on the left By following close to the aorta toward the under surface of the arch the ductus, as large as the aorta itself, will be seen as the first vessel to the left pointing upward and a little to the right. Both pulmonary branches lie too far posteriorly to be seen, and by keeping close to the aorta the main pulmonary trunk will escape injury. On pushing through the tissues by blunt dissection the ductus, theoretically, should be easily surrounded by a ligature It is a question whether or not simply crushing it would not accomplish as much, and in case of necessity, I believe that it would be worth trying. After closing the anterior pericardial wound the sternum can be sutured or not and the skin closed "[20]

It was not, however, until 1939, thirty-two years after Munro's article appeared, that Gross and Hubbard reported the first successful surgical closure of the patent ductus.[13]

COARCTATION OF THE AORTA

Apparently the first published instance of coarctation of the aorta is a case which Morgagni in 1761 reported from his correspondence.[19] The recorded description supports the supposition that accessory congenital defects were present, although no mention of them was made.

In 1791, thirty years later, Paris recorded another instance of coarctation of the aorta disclosed at postmortem examination in 1789.[21] While the early literature contains numerous publications dealing with isolated instances, many of them are based solely on postmortem findings. Among the authors of these reports are such contributors as August Albrecht Meckel (1827),[18] Reynaud (1828),[23] Cruveilhier (1835),[9] and Chevers (1845),[8] to mention only a few. It was Meckel who first called attention to the erosion of the ribs which results from the pulsations of the dilated and tortuous intercostal arteries which serve as collateral communications between the upper and lower segments of the obstructed aorta.[18]

It was not, however, until 1903, when Bonnet carefully reviewed his cases and those in the literature, that the present-day classification of coarctation came into being. Bonnet classified two basic types. The "infantile type" represents a persistence of, or exaggeration of, conditions prevailing in the fetus before birth. Here a constriction with a long segment of narrowing of the aorta occurs between the origin of the left subclavian artery and the insertion of the ductus arteriosus. It is frequently associated with other congenital anomalies of the heart. The "adult type" has no counterpart in the fetus and is represented by a marked constriction or obliteration of the aorta adjacent to, or near the insertion of, the ductus arteriosus or the ligamentum arteriosum, as the case may be. The obstruction is usually limited to a short segment of the aorta.[5]

The long obscurity of this congenital anomaly has ended with relative suddenness. Wernicke of Berlin, for his discussion of coarctation of the aorta in 1875, had discovered only five cases in the literature prior to that time in which the correct diagnosis had been made during the life of the patient.[26] Abbott in 1915 had discovered only twelve such instances.[1] Thus it is within approximately four decades that a rarely identified clinical entity has become one of fairly common-place recognition.

SO-CALLED TETRALOGY OF FALLOT (LA MALADIE BLEUE)

The casual student of medical history frequently is confused by the eponymic designation of diseases. This is vividly demonstrated in the case of Pick's disease, where three different clinical entities were described by three different physicians all bearing the name of Pick and each dissimilar disease bearing the title of Pick's disease. Examples of this are found in the history of congenital anomalies of the heart and great vessels

Etienne-Louis Arthur Fallot (1850-1911), of Marseille, in 1888 published a remarkably accurate account of a set of congenital anomalies of the heart and great vessels which he designated as *la maladie bleue.* The following quotation, in translation, is from the conclusions of his classic article:

> "This malformation constitutes a true anatomicopathologic type represented by the following tetralogy: (1) stenosis of the pulmonary artery; (2) interventricular communication; (3) rightward deviation of the origin of the aorta, (4) hypertrophy, almost always concentric, of the right ventricle;—and to these may be added sometimes, but in a strictly accessory manner, the failure of occlusion of the foramen ovale."[10]

Fallot's publication received wide acclaim, and it was not long before the combination of anomalies became known universally as the "tetralogy of Fallot." Perhaps because few modern medical authors on the subject saw fit to delve into the earlier literature or perhaps because of Fallot's brilliant account, his name continues to be usually the only one associated with this condition.

It is of unusual interest that the first known record of this combination of congenital anomalies was published in 1673 by Niels Stensen or Nicholas Steno (1638-1686), the eminent Danish anatomist, whose observations were conducted during the course of his dissection of a fetal monster. The

modern rediscovery of this case is credited to Professor Erik Warburg of Copenhagen, who kindly forwarded a copy of his report to me. The following quotation from Stensen's report is of interest:

"Most of all, the unusual form of the arteries proceeding from the heart merited both attention and amazement. At the first view, portending something strange, the pulmonary artery appeared much more narrowly constricted than the aorta; therefore I laid it open from the right ventricle of the heart to the lung itself, and at once saw plainly that the canal which leads from the pulmonary artery to the aorta (ductus arteriosus), quite evident in all other fetuses, was entirely missing.

"But when I opened the right ventricle the probe, being passed upward along the septum, found an aperture opening directly into the aorta just as easily as it soon passed upward to that very aorta from the left ventricle.

"Thus there were three openings in the right ventricle—one from the auricle, two into the arteries; and the same aortic canal common to both ventricles had twin orifices divided by the septum of the heart. In the auricles nothing differed from the usual fetal conformation."[17]

That hypertrophy of the right ventricle was not a feature of this case was probably due to the fact that the subject did not live beyond birth.

In 1761, Morgagni[19] in his *De Sedibus* described a somewhat similar case which many authors have discussed, but it does not meet the requirements for inclusion as a typical example of the tetralogy.

An early and complete description of the classic combination was published in 1777 by the famous Dutch physician, teacher and linguist, Eduard Sandifort (1742-1814) of Leyden.[4] His account was comprehensive and included all the cardinal factors enumerated by Fallot 111 years later.

In 1784, only seven years after Sandifort's classic account, the great William Hunter (1718-1783) of Glasgow and London published his observations from the postmortem examination of a child who had lived thirteen years. In his report, hypertrophy of the right ventricle is not mentioned, but the ensuing quotation is of interest.

There was a singular conformation of the heart, which allowed only a very small portion of the blood to pass through the lungs That peculiarity was partly in the pulmonary artery, which was so small at its beginning from the right ventricle, that it would barely give passage to a small probe . But there was another peculiarity—*viz* the *septum cordis* was deficient, or perforated at the basis of the heart, so as, in the dead body, to allow my thumb (a small one) to pass across, from either ventricle to the other, the orifice of the aorta being situated so close to this perforation, as, in the action of the heart, to receive the blood from the right ventricle as well as from the left."[15]

Other early accounts of this tetralogy, selected through analysis of published reports, were given by Cailliot in 1807,[10] Pallois in 1809,[10] and Gintrac in 1824[10]; and the frequency of such publications increased as the year of Fallot's description approached.[10]

Worthy of mention is Thomas Bevill Peacock (1812-1882) of London, who in 1866 published the second edition of his classic work, *On Malformations of the Human Heart* This, incidentally, was the first book on con-

genital anomalies of the heart to be published. In this volume, Peacock described more than eighteen cases, nine of which were typical examples of the tetralogy.[22]

It is evident that numerous observers—some very early—had accurately described the congenital derangement responsible for *la maladie bleue* before Fallot's description appeared in 1888. In this presentation there is no intention whatsoever to detract from the recognized prestige of Fallot's publication, but in historical documentation the correct sequence of priority should be maintained.

UNCOMPLICATED SEPTAL DEFECTS

The general conformation of the fetal heart and the foramen ovale were first described in 1593 in a volume by the same Giambattista Carcano who studied the ductus arteriosus, but the foramen and the septum which normally replaces it were not immediately understood.

In 1640, Pierre Gassendi (1592-1655) of Champtercier, France, later a professor at Aix, with three other authors published a book in which Gassendi's contribution was an account of the demonstration of a patent foramen ovale at postmortem examination of an adult. Gassendi was not the discoverer but a witness—and indeed, it should be repeated that he and presumably his colleagues interpreted the findings as proof of an erroneous theory of circulation. Gassendi wrote, in translation:

"While I was residing in Aix, whenever a dissection was being performed I was present frequently in the anatomical amphitheatre. Now for many years I had observed invariably that dissectors, taking the heart in their hands, would test the perviousness of its septum with a blunt instrument which they call a spatula, and would conclude, as physicians have concluded, that the transmission of blood from the right chamber to the left must occur by insensible transudation Now when this problem came to be discussed by the professors of anatomy, eight years ago, there came among the disputants a diligent surgeon, Payanus by name, who wanted to demonstrate to us onlookers that the facts were otherwise So, taking up the spatula, he undertook to penetrate the mediastinum of the heart. But he did not attempt to push the instrument straight through, as the others had done, but having introduced its tip (for the tissue of the septum presents a thousand little openings) pushed onward with utmost gentleness, turning the instrument with the greatest patience up and from side to side, seeking always a farther ingress and at last the instrument was seen entering the left chamber But then, because we had alleged that he had made an artificial opening, he himself requested one of us to incise the septum down to his instrument, with a sharp scalpel. When the incision had been made we found that no tissue anywhere had been injured, and we saw that only the meatus, or canal, notwithstanding the fact that it was a very winding passage, was lined with a very thin and glistening membrane."[11]

Allan Burns (1781-1813) of Glasgow, a little-known contributor to the records of medical history, published a significant work in 1809. Among the cases of congenital anomalies of the heart which he discussed were instances in which the foramen ovale and the ductus arteriosus were open, others in which only the foramen ovale was open, and others in which a defect in the interventricular septum occurred.[6]

One of the most important and outstanding contributions dealing with septal defects was that of the brilliant Bohemian pathologist, Carl Rokitansky (1804-1878), for many years Professor of Pathology at Vienna In 1875, after fourteen years of investigation, Rokitansky published his important volume dealing with septal defects and his theory of their genesis. He showed that the ventricles in their development are separated from each other by the upward growth of the septum, and that the common arterial trunk is also separated into right and left halves by a septum having its origin in an indentation in the walls of the vessel. The septum of the ventricles and the septum between the two halves of the arterial trunk become joined, so that each ventricle finally communicates with one half of the vessel. Normally, a rotation of the arterial ends of the ventricles and the great arterial trunk occurs so that the portion of the trunk which is to become the pulmonary artery is in front and to the left of that portion which is to become the aorta. If in the course of development this process of rotation fails to occur prior to the union of the ventricular and aortic septa, it remains possible for the aortic portion of the trunk to open into the right ventricle, while the pulmonary portion communicates with the *left ventricle*.[25]

In 1861, while performing a postmortem examination, Henri-Louis Roger (1809-1891) of Paris demonstrated the presence of an interventricular septal defect in the absence of stenosis of the pulmonary artery.[24] Eighteen years later (1879), Roger published his classic article dealing with the characteristic physical signs of the uncomplicated interventricular septal defect. The following translated excerpt from his article is of interest·

> "The condition is revealed only through auscultation, and is evidenced by a physical sign whose characteristics are wholly peculiar—a strong and lengthy *murmur*. It occurs quite alone, begins with systole, and continues so long as to overspread entirely the normal 'tic-tac' sounds It is greatest not at the apex (as with lesions of the auriculoventricular orifices), nor at the right of the base (as with stricture of the aorta), nor at the left (as with stenosis of the pulmonary artery), but in the upper third of the precordial region It is medial, like the septum itself; from the focal point its intensity diminishes regularly by degrees in proportion with the increase of distance; the location is fixed, and there is no propagation in the vessels It coincides with no other *sign of morbid organic condition except purring tremor An anomalous* murmur in which this group of characteristics is combined is *the pathognomonic sign of patency of the interventricular septum*."[24]

Even today, this characteristic murmur is known as the "bruit de Roger."

The most extensive contributor to knowledge pertaining to congenital anomalies of the heart and great vessels was Maude E. Abbott (1869-1940) of Montreal. Among many publications her greatest work was the remarkable *Atlas of Congenital Cardiac Disease.* This volume, which appeared in 1936 under the sponsorship of the American Heart Association, contains a critical analysis of 1,000 cases.[2]

Maude Abbott's teaching and writings were the most outstanding factors in converting the mysteries and uncertainties of congenital anomalies

of the heart and great vessels into understandable realities. Through her work and influence the clinical diagnosis of the various defects has become remarkably precise and thus has enabled the surgeon to intervene, so that an ever-increasing number of hitherto incurable patients are now finding relief.

From this historical review it is evident that our medical forebears have built the basic structure of cardiology wisely and well. Without this foundation of knowledge at their command, present-day scientists could not possibly have achieved the amazing progress of the last two decades.

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5B

Congenital Cardiovascular Abnormalities

Incidence:[1] Reports of congenital cardiovascular defects found at necropsies would indicate that among the population at large the incidence is approximately 1 per cent, the greater number of cases naturally occurring in early childhood. The incidence of cardiac anomalies among infants dying before the age of two years was 4 per cent and among individuals ranging from two years through adult life 0.7 per cent. In a study of the incidence of congenital malformations in over 5000 pregnancies, defects of the cardiovascular system were found in 0.9 per cent of total births. At all ages, including the neonatal period, individuals with persistent cyanosis due to cardiac defects are fewer in number than those who present no cyanosis

Etiology: Under normal conditions the embryonal cardiac tube passes through a series of coordinated changes in its progress toward the four-chambered human heart. These include division into four primitive chambers; rotation of the tube upon itself so as to conserve space; absorption of the sinus venosus into the atrium and the bulbus cordis into the ventricle; separation of the primitive atrium, primitive ventricle, and truncus arteriosus by the formation of septa and valves.

The majority of cardiac anomalies result from arrest in this coordinated process of development. The earlier in embryonal life this occurs, the more complicated the anomaly. If before the fifth week of fetal life, a nonviable monstrosity results. Interruption of normal development of the heart between the fifth and eighth weeks will result in a viable infant born with an abnormal heart. The graver anomalies of the cyanotic group take origin in the earlier part of this period when division of the atrioventricular canal and truncus arteriosus is proceeding concurrently with shifting and rotation of these parts upon themselves in the median axis of the heart while involution of the primitive bulbus cordis is taking place. By the end of the eighth week of fetal life the septa have closed.

The relative frequency of associated anomalies elsewhere in the body bears out the belief that malformation of the heart is due largely to factors which have disturbed the normal course of development rather than to localized inflammatory states. Since the fundamental structure of the heart is established by the eighth week of fetal life, such factors must have been operative in the early weeks of pregnancy. Studies have emphasized the importance of environmental factors in producing malformation of

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the fetus. Experimentally, cardiovascular malformations in the fetus have been produced by a diet deficient in vitamins fed to pregnant animals and by exposure of the embryo to irradiation, hypoxia, trypan blue, or to an atmosphere high in carbon dioxide.[2] Nutritional deficiencies of the fetus may be due not only to dietary deficiencies of the mother but perhaps also to maternal or placental diseases. Renal disease, endocrine disorders, even emotional disturbances may play a part. At least one disease of viral origin has been incriminated. Infants of mothers who developed rubella within the first three months of pregnancy have been born with cardiac anomalies which may be associated with congenital cataract, congenital deafness, or mental retardation. In the experience of the writer, severe vomiting or significant bleeding in the first trimester has occurred as frequently as viral diseases in the history of mothers who have given birth to children with cardiovascular malformations. Syphilis rarely if ever plays an etiologic rôle. Unsuccessful attempts to induce abortion early in pregnancy have been admitted by some mothers. In the majority of cases, however, no history of maternal disturbance in health can be obtained.

That an hereditary tendency may play a part is suggested by the occasional association of conditions of known familial origin, such as polydactylism or arachnodactyly, as well as by the appearance of cardiac anomalies in more than one generation, in siblings or in collateral branches of the family. What advice as to future progeny should be given to parents of a first child born with a defective heart? In the case of young parents it would seem wise to encourage a second pregnancy. Granted that the chance of producing another abnormal child is greater than the average, in the majority of instances subsequent offspring will be normal. Since the proportion of defective children becomes progressively greater as the age of the mother increases, contrary advice should probably be given to parents past the age of thirty.

After birth, anatomic closure of the ductus arteriosus and foramen ovale is gradual rather than abrupt. Gradual reduction in the caliber of the ductus culminates in obliteration not earlier on the average than six to eight weeks after birth. Following functional abandonment of the foramen ovale, adhesion between the septum and valve takes place slowly and is usually not complete until the latter half of the first year. The isthmic portion of the aorta lying between the left subclavian artery and the ductus arteriosus, which in the fetus is normally narrow, requires a period of approximately two months to reach the full caliber of the contiguous parts of the aorta. The finding of some degree of narrowing of the isthmus or of patency of the ductus arteriosus or foramen ovale within the period shortly following birth should not be interpreted as abnormal. Although anatomic closure is gradual, functional closure of the ductus arteriosus and foramen ovale may take place shortly after birth.

Classification: The following classification suggested by Dr. Maude E. Abbott[3] based on the presence, absence or late appearance of cyanosis has proven of value. It has been modified by the author on the basis of recently developed hemodynamic concepts.

Group I—Acyanotic: Lesions in which no communication exists between the arterial and venous circulation. Admixture of venous and arterial blood does not occur. Pulmonary flow equals systemic flow. Cyanosis appears only in the presence of heart failure and is due to peripheral stasis.

Group II—Arteriovenous Shunt: Lesions in which there exists a communication between arterial and venous circulations without the presence of a complicating anomaly that might alter the normal pressure relations within the heart. Under normal conditions of pressure the shunt will be arteriovenous and the pulmonary flow will be greater than the systemic flow. In the presence of pulmonary hypertension due to occlusive changes within the intrapulmonary arteries there may be a reversal of flow and the appearance of cyanosis. This may be preceded by a period of balanced pressure during which the flow may be bidirectional.

Group III—Cyanotic: Anomalies which ensure the mixture of venous and arterial blood within the heart or which prevent adequately oxygenated blood from entering the systemic circulation Anoxemia exists at birth although not always of a degree sufficient to be visible as cyanosis in the neonatal period. The lungs may receive an excessive, normal, or inadequate supply of blood depending on individual variations in the structure of the cardiovascular anomalies which are included in this group.

Pathogenesis of Congenital Cyanosis: Lowered oxygen saturation of the blood which reveals itself clinically by the appearance of cyanosis may be the result of a variety of causes acting singly or in combination. In their classic monograph on cyanosis, Lundsgaard and Van Slyke[4] outlined the following primary factors responsible for its production: (1) Diminished oxygenation within the lungs; (2) direct venous-arterial shunt in the presence of an anomalous defect; (3) increased utilization of oxygen within the peripheral circulation as a result of stasis; (4) high hemoglobin level. All of these factors may play a part in the production of cyanosis in the individual with a suitable cardiac anomaly. Hitherto the part played by diminished oxygenation within the lungs has been thought to be due mainly to secondary factors such as the development of pathologic changes within the walls of the alveoli or pulmonary capillaries which might hinder the penetration of oxygen into the blood. Taussig[5] has emphasized the primary part that inadequate pulmonary circulation itself may play in the production of cyanosis. Such diminution in pulmonary blood volume may occur in the presence of anomalies which hinder the exit of blood from the right ventricle. The volume of blood passing through the lungs may be so reduced as to diminish oxygenation to a point insufficient for the maintenance of life.

Arterial anoxemia may be present even in the absence of visible cyanosis. At least 5 Gm. of reduced hemoglobin per 100 cc. of blood in the peripheral vessels are necessary to produce cyanosis. The appearance of severe anemia may efface a preceding cyanosis even though the degree of oxygen unsaturation is still high. With equivalent values of oxygen unsaturation, cyanosis will be less marked in the individual with a normal blood count than in the individual with polycythemia. The intensity of

cyanosis in itself thus is not an indication of the extent of anoxemia from which the individual may be suffering.

In addition to the factors which are directly responsible for the production of anoxemia, other modifying factors may influence its visibility in the form of cyanosis. Such are thickness of epidermis; variations of skin pigment; and number, size, and distribution of skin capillaries. The ability to detect slight cyanosis varies also with the skill of the individual observer.



FIGURE 1. Clubbing of fingers in a nineteen-year-old boy with cyanosis

Polycythemia may precede cyanosis. Some individuals, however, even though definitely cyanotic and with greatly lowered oxygen saturation, may show delay in the development of compensatory polycythemia. One such cyanotic infant seen by the writer at the age of eleven months, with an erythrocyte count of 4,870,000 and a hemoglobin content of 12.5 Gm., was sufficiently anoxemic to be subject to daily attacks of unconsciousness. Her arterial oxygen saturation was 41 per cent. One therefore cannot assume that the prognosis in a cyanotic individual is more favorable in the absence of marked polycythemia nor that the degree of anoxemia will be small. *Clubbing* always follows cyanosis (Fig. 1).

Cases of congenital cyanosis offer excellent opportunities for the study of the adaptation of the body to high grades of oxygen unsaturation. Such a case study has been reported by Talbott[9] and his associates with a summary of previous observations. Individuals with congenital cyanosis showed blood gas concentrations that deviated consistently from the

normal. Such deviations included increased oxygen capacity, decreased oxygen saturation, and decreased carbon dioxide content of the arterial blood; decreased partial pressure of alveolar carbon dioxide; and decreased arterial pH. The metabolic investigations on Talbott's patient revealed profound variations from the normal in the acid base equilibrium Studies on arterial blood gases and acid base balance in sixty cyanotic congenital cardiacs by Morse and Cassels[7] have confirmed these findings. The alkaline reserve of the plasma was reduced in two-thirds of the cases due mainly to fixed acid excess and CO_2 deficit. By means of the high oxygen capacity due to increased hemoglobin the oxygen content of the arterial blood was maintained within normal range in all but 15 per cent. In a group of forty-five cyanotic congenital cardiacs studied by Holling[8] an additional compensatory mechanism seemed to be the passage of oxygen from blood to tissues at pressures of oxygen lower than normal.

Cyanotic congenital cardiacs show an increased circulating blood volume due to increased rise in the volume of circulating red blood cells. There is a reduction in plasma volume. The red blood cells are normal and contain hemoglobin of the adult type. Polycythemia may mask a nutritional anemia. If the level of hemoglobin is not commensurate with the erythrocyte count, the administration of iron is advisable.

Blood samples obtained postoperatively after pulmonary blood flow had been increased by aortic-pulmonary anastomosis or by pulmonary valvotomy showed marked rise in alkaline reserve and arterial pH, in addition to an increase in arterial oxygen saturation and decrease in oxygen capacity.[7] The subnormal plasma volume rises to a level slightly higher than normal while the greatly elevated red blood cell volume is reduced to a level which may still be somewhat above the normal average.

Pulmonary Hypertension:[9] Normally the pressure in the pulmonary circuit is about one-quarter to one-fifth that in the systemic circuit, and pulmonary flow equals systemic flow. When normal pressure relationships prevail and a communication exists between the systemic and pulmonary circulations the shunt through the defect will be arteriovenous The size of the shunt and the rate of pulmonary flow vary primarily in accordance with the size of the defect. If the defect is small the shunt will be clinically insignificant. With larger defects the shunt may be large. Because of the distensibility of the pulmonary vascular channels, flow may increase up to three times normal without increasing pulmonary pressure Beyond a certain critical level of pulmonary blood flow, however, a rise of pressure may occur which at first is only slight or moderate.

Only a mild degree of pulmonary hypertension can be produced solely by increased pulmonary flow. Severe pulmonary hypertension develops as a result of increased pulmonary resistance due to anatomic changes within the small arterioles of the lungs which reduce the size of the lumen. As a result, pulmonary pressure will rise until it becomes equal to and finally greater than systemic pressure. At this stage, reversal of flow occurs (at first only during exercise) leading to a venoarterial shunt and the appearance of anoxemia and cyanosis. With progressively increasing pulmonary vascular resistance the blood flow within the lungs decreases and may be so

greatly reduced as to diminish oxygenation to a point insufficient for the maintenance of life.

Patients with pulmonary hypertension of significant degree show anatomic changes in the intrapulmonary arterioles. These changes are of two types: (1) medial thickening, and (2) intimal fibrosis often with superimposed thrombosis. The pathologic physiologic processes responsible for these changes and their relation to increased pulmonary flow are unknown. Whether the thickening of the media is due to anatomic hypertrophy of the muscular layer or to vasoconstriction is also uncertain. Because of the small pressure differential between the two atria, pulmonary hypertension resulting from an atrial defect is due solely to the size of the flow and to secondary intimal changes within the pulmonary arterioles. In the case of a ventricular septal defect, however, or of an aortic-pulmonary communication such as a patent ductus the defect connects a region of high pressure with one in which the pressure is only one-fifth as great. A very large ventricular defect or patent ductus which presents little or no resistance at the site of the lesion provides free communication between the arterial and venous circulations. Blood will be ejected into the lungs under systemic pressure. The systolic pressure will be equal in both ventricles, the aorta and the pulmonary artery. Flooding of the lungs with blood can only be prevented by increased intrapulmonary resistance and a rise in diastolic pressure.

In the fetus there is a high level of resistance to pulmonary blood flow due to the structure of the muscular arterioles which have a thick wall and narrow lumen. Thickening of the medial musculature is found in these vessels. Normally a gradual change takes place within the first six months of life so that the wall becomes thin, the lumen wide, and resistance to blood flow low. Similar thickening of the medial layer of the intrapulmonary arterioles occurs in the presence of a large ventricular septal defect or patent ductus and has been ascribed to postnatal persistence or development of fetal type vessels in order to maintain high resistance in the pulmonary circuit and thus permit an adequate amount of blood to enter the systemic circulation. Closure of congenital defects at this stage may be followed by thinning of the vessel walls similar to that which occurs under normal postnatal conditions.

Intimal fibrotic thickening which may sometimes be associated with organized emboli or thrombi is probably of postnatal origin and irreversible. It results in further narrowing of the vessels and progressively increasing hypertension. It may be found in vessels which show medial thickening as well as in vessels which seem to have been normal originally. When the intrapulmonary arterioles are markedly narrowed and pulmonary resistance high, the volume of blood within the lungs is diminished and may be normal or less than normal even though the communicating defect is large. At this stage surgical closure is contraindicated since the defect itself may be serving as a safety valve.

There is no direct relation between age and pulmonary hypertension Pulmonary pressure may be very high in some infants or young children and may remain normal in adults even with large shunts.

There is no good explanation for the persistence of pulmonary hypertension and vascular changes in the patient who has no communication between the pulmonary and systemic circuit. Nervous factors have been incriminated.

Symptoms and Prognosis: A minority of infants with congenital cardiac anomalies tend to be slow to gain weight, delayed in growth and development, and subject to digestive disorders. Lowered resistance to infection is especially common among such malnourished children and conversely the prognosis is far more favorable among infants whose nutrition and development have not been hampered by the cardiac lesion. In later life these individuals may remain dwarfed and of fragile build, but frequently a spurt of growth occurs as puberty is reached.

The natural death rate is greatest in the first two years of life, only in part due to death of cyanotic babies with malformed hearts not capable of maintaining postnatal circulation. There is a high death rate among babies with large ventricular septal defect; short, wide patent ductus; common arterial trunk from which a large pulmonary artery arises; or with a single ventricle which supplies the common ejectile force for both the systemic and the pulmonary circulation. In all of these malformations the lungs are flooded with a large volume of blood under systemic pressure. They may all lead to a similar clinical picture of repeated respiratory infections, progressive emphysema, cardiomegaly associated with respiratory distress, pulmonary edema with or without hepatomegaly. Death occurs also in infants with the left ventricle supplied by a coronary artery arising from the pulmonary artery, or with endothelial fibroelastosis. A fair number of infants with coarctation of the aorta may die of congestive failure

After the second year of life the rate of death becomes minimal in the noncyanotic child Noncyanotic school children with congenital cardiac anomalies rarely present symptoms. In a relatively small group with lesions permitting an excessive shunt of arterial blood into the pulmonary circulation, the increased volume of blood in the lungs may result in tachypnea and the inadequate peripheral circulation may produce fatigue and stunting of growth. The expectation of life in noncyanotic individuals is usually good in so far as the defect itself is concerned, although some cardiac strain is present and must be taken into consideration as a factor liable to produce heart failure in early adult life. A good tolerance for exercise even in the presence of a greatly enlarged heart is a striking characteristic, however. Complications, such as bacterial endocarditis, usually delay their appearance until adult life.

Certain special symptoms may be associated with individual lesions Because of the tremendous dilatation of blood vessels in the upper part of the body individuals with coarctation of the aorta may suffer from headaches, epistaxis or pains in the chest or shoulders. Intermittent claudication may result from inadequate circulation in the legs. Sudden death may be due to rupture of the aorta or of a small cerebral aneurysm. In the presence of right or double aortic arch, dyspnea or dysphagia may occur from pressure of the encircling ring upon the trachea or esophagus.

Pressure upon the recurrent laryngeal nerve by a dilated pulmonary artery may produce hoarseness or aphonia. Individuals with severe pulmonary hypertension are subject to chest pain and recurrent attacks of hemoptysis. The occurrence of Stokes-Adams attacks in congenital heart block has been reported.

The presence of congenital defects elsewhere in the body is not uncommon, as is mental deficiency, which may be associated with mongolism. On the other hand, many congenital cardiacs, including those with cyanosis, have a high level of intelligence.

In subjects with congenital cyanosis the course is progressively downward, the duration of life depending upon the nature of the defect and the amount of interference with oxygenation which it imposes. In the graver cyanotic cases, death usually occurs at an early age from the mechanical difficulties of the circulation. In contradistinction, a not inconsiderable group of individuals with less severe lesions of the cyanotic type has been able to lead long and even arduous lives. Cyanotic women have given birth to normal infants. In all cases, however, with permanently lowered oxygen saturation of the blood due to structural changes within the heart or great vessels, a vicious cycle is engendered which ends sooner or later in death from anoxemia of the tissues, unless life has been shortened by an intercurrent complication.

Infants with lesions of the cyanotic type need not be blue babies. As the requisite threshold of oxygen unsaturation is passed, however, cyanosis makes its appearance—first visible as a bluish discoloration of the lips and fingertips; later deepening in intensity and spreading over the entire surface of the skin and mucous membranes; accentuated by cold temperatures and by muscular exertion. Polycythemia may precede cyanosis and increase as the anoxemia increases. Clubbing of fingertips (Fig. 1), toes, and nose follows cyanosis after varying intervals of time. Tortuous, thick-walled capillaries and violet discoloration become visible in the retinae. Squatting is a common habit among cyanotic children suffering from an inadequate flow of blood to the lungs. Dyspnea, attacks of which may occur even before cyanosis is apparent, may culminate in seizures of extreme respiratory distress, associated with marked exacerbations of cyanosis. Epileptiform seizures or syncopal attacks are not uncommon, especially when the red blood cells are extraordinarily increased. Cerebral thrombosis with hemiplegia may be terminal. An important complication in cyanotic individuals with right to left shunt is the passage of a paradoxical embolus through the anomalous opening to lodge in brain, spleen, kidney, etc. Such an embolus if infected may form the focus for the development of a brain abscess which probably occurs as frequently in cyanotic congenital cardiacs as does endocarditis. Fatal gastrointestinal hemorrhages have been observed in cyanotic infants who presented no ulcerative lesions at necropsy. Presumably the bleeding was due to increased capillary permeability of anoxic origin.

Congestive failure is the most frequent cause of death in adults with cardiac anomalies. Despite these dangers that lie in wait for the individual

born with a defective heart, many such persons have been able to lead long and useful lives.

Diagnosis: The existence of a cardiac anomaly is obvious in the relatively rare individual who presents cyanosis and clubbing associated with abnormal cardiac signs. It may, however, fail to be recognized in the noncyanotic individual. In the infant past the neonatal period the presence of an intense murmur not associated with marked anemia is usually indicative of the existence of an abnormal heart. Newborn infants whether or not they are cyanotic may present murmurs which disappear and are not associated with cardiac anomalies. On the other hand it is possible for the heart to appear normal at birth in infants who later develop a cardiac murmur associated with other signs of congenital heart disease. In older noncyanotic children and adults a congenital lesion may be suspected when a systolic murmur is heard best to the left of the sternum rather than at the apex, where the murmur of an acquired mitral lesion is best heard. The presence of a thrill and of cardiac enlargement would confirm the existence of an organic lesion. In the absence of murmurs, unusually loud clanging heart sounds may at times arouse suspicion.

Once the presence of a cardiac anomaly is accepted, the differentiation of the particular lesion is a more difficult task. In the graver complicated lesions of the cyanotic group an exact diagnosis may be impossible, particularly in the young infant.

Probably the only cardiac abnormality associated with a pathognomonic *electrocardiogram* is mirror image dextrocardia, in which all complexes of Lead I are inverted and the curves of Leads II and III replace each other. An exact diagnosis of congenital heart block can only be obtained by graphic methods, but the existence of heart block does not point to any specific anomaly such as ventricular septal defect, since interruption of the bundle of His by fibrous tissue may be found in an otherwise normal heart. The tracing obtained from an individual with a cardiac anomaly may be entirely normal. If abnormal, it need not differ from one due to acquired disease. In early life, however, the presence of biphasic QRS complexes, if splintered or prolonged, or of right or left ventricular preponderance should suggest the possibility of a congenital defect. Information obtained from precordial leads may be of greater value than the roentgenogram in the determination of predominant right or left ventricular enlargement. Such information, however, is inferential only and may at times be misleading Recent studies have attempted to define electrocardiographic variations due to systolic and diastolic overloading of the right or left ventricle.[10] Attempts are being made to correlate such changes with specific congenital cardiac lesions.

Since an enlarged right atrium is common in congenital heart disease, the frequent finding of high P waves is not unexpected.

Inversion of T waves in the electrocardiogram of infants with cardiac enlargement has been stated to be indicative of the presence of an anomalous left coronary artery arising from the pulmonary artery. Negative T waves of varying contour, however, may be found not only in association with an anomalous coronary artery, but also in glycogen storage disease,

endothelial fibroelastosis, as well as in infants with cardiomegaly and congestive failure of unknown origin not necessarily fatal.

Roentgenograms:[11] Scalloping of the lower border of the posterior ribs occurs most frequently in the presence of coarctation of the aorta. The existence of anomalous retroesophageal vessels, of right sided or double aortic arch, and of dextrocardia may be established by roentgenographic means. Aside from these it is rarely possible to diagnose a specific anatomic defect from routine roentgenograms unaided by other information. Identical changes in contour may be produced by dissimilar lesions; the same lesion may produce dissimilar alterations in the cardiac shadow in different individuals; finally, the heart may be normal in size or contour even though an anomaly exists. Criteria for individual chamber enlargement in acquired heart disease are not necessarily applicable to cardiac anomalies where the fundamental configuration of the heart may bear no resemblance to the usual four chambered heart.

Anomalies associated with an arteriovenous shunt will result in dilatation of the pulmonary artery and its branches due to the increased volume of blood sent to the lungs. Evidence of such enlargement of the pulmonary vascular tree will be revealed by increased fulness of the pulmonary segment together with large, sharply delineated hilar shadows and prominence of the smaller vessels in the middle third of the lung fields. In contrast, the presence of a venoarterial shunt will result in diminution of the amount of blood sent to the lungs, and decrease in size of the hilar shadows with diminished vascularity in the peripheral lung fields.

Roentgenograms taken in various positions together with fluoroscopic examination are of value in revealing alteration in size and contour of individual chambers of the heart and great vessels, as well as variations in the hilar and intrapulmonary vascular shadows. Correlation with clinical and electrocardiographic findings may lead to a correct diagnosis of anatomic defects. The characteristic roentgenographic changes will be described in the discussion of individual lesions.

Angiocardiography:[12] Consists of the roentgenographic visualization of the cardiac chambers and great vessels following the rapid injection of a radiopaque fluid into a peripheral vein. Serial roentgenograms are obtained while the contrast substance is passing through the heart and great vessels. The most readily available commercial machine takes two roentgenograms per second. Angiocardiograms may at times provide valuable diagnostic information. Particularly in young infants and children, however, the passage of contrast substance occurs so rapidly as to visualize the entire heart within a second or less. It is often impossible to follow the sequence of events and to make an accurate anatomic diagnosis. The maximum potential value of this procedure will not be obtained until a practical and not too expensive apparatus is developed by means of which at least ten roentgenograms per second may be obtained simultaneously in two planes at an exposure time of $\frac{1}{250}$ second with electrocardiographic control. Such an apparatus is available, but at a cost beyond the reach of the average institution.

Regional angiocardiography has been developed with the aid of an intra-

cardiac catheter placed at a selected site, forced injection of contrast substance, and short exposure time. For example, with the catheter placed in the right ventricle it is possible to ensure good visualization of the infundibulum and pulmonary valve. With the catheter placed in either the right or left pulmonary artery accurate information can be obtained as to the existence of anomalous pulmonary venous drainage from either lung.

Retrograde Aortography: When good visualization of the aorta is essential the radiopaque substance may be injected directly into the brachial artery or through a catheter inserted into the exposed brachial, external carotid, or femoral artery. Visualization of the site of coarctation or of the passage of contrast substance from the aorta through a patent ductus or aortic septal defect may thus be obtained.

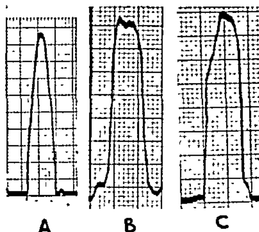


FIGURE 2 Pressure tracings from right ventricle. A, Pulmonary stenosis with intact ventricular septum, peaked symmetrical curves B, Pulmonary stenosis with ventricular septal defect: asymmetric curve with rapid ascent and plateau top C, Pulmonary hypertension: initial rapid upslope followed by more gradual rise to a peak after which there is rapid descent to the diastolic level

Cardiac Catheterization: Samples of blood are obtained by directing a catheter, usually inserted through the median basilic or saphenous vein, into various regions of the heart and great vessels under fluoroscopic control. Samples thus obtained by venous catheterization and by direct puncture of the femoral artery may be compared for oxygen and carbon dioxide content. Pressures may be measured in the great veins, the cardiac chambers, and the pulmonary artery. The rate of oxygen consumption and carbon dioxide elimination is determined by indirect calorimetry. With data thus obtained the cardiac output may be calculated by the Fick principle. With the use of suitable formulae an estimation may be obtained of the volume of blood flow through the pulmonary artery, the systemic circulation, and through intracardiac shunts.

Pressure tracings taken from the right ventricle during cardiac catheterization show differential features. (See Fig 2.) Curves from a ventricle which has no adequate outlet, as in the case of severe pulmonary stenosis

and intact ventricular septum, have a peaked symmetrical appearance, whereas in the presence of a ventricular septal defect the curves resemble those obtained from a ventricle with a normal valvular outlet. They are asymmetric with a rapid ascent and plateau top.[13] Curves from the right ventricle of patients with pulmonary hypertension tend to show an initial rapid upslope, followed by a more gradual rise to a peak after which there is rapid descent to the diastolic level.[14]

The information provided by venous catheterization can be of great diagnostic value. The finding of a significantly higher content of oxygen in blood from the right atrium or right ventricle for instance points to the presence of an arterial venous shunt into these chambers. The specific findings that may be noted in association with individual cardiac anomalies will be described later in a discussion of these lesions.

Methods have been devised whereby it is possible to perform cardiac catheterization and selective angiocardiography in a single-stage procedure with the simultaneous use of high-speed motion picture photography.[15]

Oximetry: The oximeter is an instrument which records the color changes due to varying amounts of reduced hemoglobin in the peripheral arteries of the ear lobes by means of a photoelectric cell attached to the pinna. It can be used to furnish a record of the changes in arterial oxygen saturation during exercise and while breathing 100 per cent oxygen.[16] In the normal individual there is no significant change in oxygen saturation when rising from the supine to the erect position or during moderate exercise. Patients with cyanotic heart disease show a decrease in oxygen saturation of about 2 per cent when changing to the erect position, and a fall of at least 10 per cent with exercise. In the normal individual the arterial oxygen saturation is about 95 per cent. During the inhalation of 100 per cent oxygen full saturation is obtained rapidly. In cyanotic patients with right to left shunts the arterial oxygen saturation is below normal. The time required to attain maximum oxygen saturation when breathing oxygen is prolonged and full saturation is not reached.

The oximeter can also be used to measure the time required for circulation of injected dyes such as methylene or Evans blue which possess absorption characteristics suitable for detection by this instrument. The dye may be injected either into the peripheral circulation or directly into the right ventricle through a cardiac catheter, and the time of arrival at the ear measured with the oximeter.

Curves obtained following the injection of dye intravenously have been found to have a typical pattern in the presence of left to right[17] and right to left[18] shunts. Localization of the shunt can be determined by intracardiac injection of the dye during catheterization.

INDIVIDUAL CONGENITAL LESIONS

Acyanotic Lesions

Pericardial Defects: These vary from complete absence of the parietal layer, as in the nonviable forms of ectopia cordis, to a more or less extensive defect of the left side of this structure, so that the pericardial

cavity communicates freely with the left pleura either by a localized opening with serous margins or by a deficiency so large that the heart and left lung come to lie in a common cavity. The left phrenic nerve is displaced to the right in a degree increasing with that of the defect, a point of value in the diagnosis of congenital origin. The pathologic significance of this condition lies in the abnormal juxtaposition of the serous surfaces of the heart and left lung which predisposes to inflammatory processes, and in the existence of a cor mobile with consequent tendency to kinking of the great vessels.

Ectopia Cordis: Rarely the heart may be displaced to the cervical region. More frequently it is extruded in the thoracic region through a fissure of the sternum or into the abdomen through a defect in the diaphragm. Combined sternal and diaphragmatic defects may be present. The only viable forms are those of pectoral heart with inferior sternal fissure and both layers of pericardium present, and abdominal heart. A case has been reported of an old soldier who died of right suppurative nephritis and who at necropsy was found to have an absent left kidney. In its place lay the heart in the pericardial sac with vessels passing into the thorax through a diaphragmatic defect. There have been recent reports of successful surgical repair of ectopia cordis situated in the thoracoabdominal region.[19]

Anomalous Bands and Chordae: These vary considerably in pathologic interest and in origin. In the right atrium a delicate fenestrated membrane or system of fine strands (*network of Chiari*) continuous with the eustachian or thebesian valves, may stretch across the cavity to be attached to the upper part of the interatrial septum or adjacent parts It represents a persistence of the valvula venosa dextra or sinistra and is of little clinical import except that it may form a nidus for thrombotic processes leading to pulmonary embolism. Anomalous chordae in the left ventricle may occur, sometimes taking origin from the walls of this cavity and sometimes extending downward through the mitral orifice from an attachment in the left or even in the right atrium. These may give rise to unusual adventitious sounds but are otherwise unimportant.

Anomalies of the Semilunar Cusps: The aortic and pulmonary cusps may be increased or diminished in number. Supernumerary cusps are commonest at the pulmonary orifice. Four or even five segments may exist and, of these, two may be congenitally fused or incompletely divided presenting a combination of both types of anomaly. Reduction in number of cusps is however more frequent than their increase. A bicuspid aortic valve may occur alone or in combination with coarctation of the aorta or subaortic stenosis. The anomaly may consist of only two segments without trace of a third. Commonly one of the two cusps presents on its arterial surface a low partly obliterated raphe which represents the contiguous margins of the combined cusps and partly divides the sinus of Valsalva behind it. The cusps are usually large, well formed, and perfectly adapted to close the arterial orifice in the absence of postnatal inflammatory processes which may lead to thickening and deformities along the line of closure, resulting in incompetence and obstruction. Isolated aortic endo-

carditis should lead one to suspect the existence of an underlying bicuspid valve of congenital origin. Bicuspid pulmonary valve is rarer than aortic as an isolated lesion. In combination, however, with hypoplasia of the pulmonary artery in tetralogy of Fallot it is a relatively common anomaly.

Small, dark-red, circumscribed nodules on the valve cusps of infants in the first months of life are due to the formation of localized *blood cysts* which become incorporated in the substance of the cusp during fetal life. They are of no pathologic importance and should not be mistaken for endocardial vegetations.

Primary Idiopathic Hypertrophy: Theoretically this should include instances of marked cardiac enlargement in infancy and early childhood due to primary hypertrophy or hyperplasia of muscle tissue. In a comparatively small number of cases the use of this term may still be warranted. Many cases of cardiac enlargement, however, which in the past were considered of idiopathic origin are now recognized to be due to such disorders as glycogen storage disease, avitaminosis, abnormalities of the coronary vessels, endothelial fibroelastosis, hypertension of the greater or lesser circulation, paroxysmal tachycardia, interstitial myocarditis. Tumors of the heart (congenital rhabdomyomata) also must be considered in the differential diagnosis.

Endocardial Fibroelastosis (Fetal Endocarditis; Endocardial Fibrosis; Endocardial Sclerosis):[20] Although some degree of endocardial thickening may occur secondarily in association with various cardiac malformations, endocardial fibroelastosis may also make its appearance in infancy as a primary developmental disturbance. In such cases the left ventricle and atrium are greatly enlarged with marked thickening of the endocardium (sometimes involving the aortic and mitral valves) due to great increase in the number of elastic fibers with slight excess of collagen. There is no evidence of inflammatory reaction. The right ventricle is rarely involved unless sclerosis and narrowing of the mitral valve is associated. If the child lives long enough degenerative changes of the myocardium may appear secondary to penetration of the sinusoids and thebesian vessels by the fibroelastic tissue.

Infants with this condition are apparently normal at birth. Murmurs are frequently absent. The electrocardiogram may show either no axis deviation or left axis deviation in standard leads but precordial leads usually present evidence of left ventricular hypertrophy. T waves may be low, diphasic, or inverted, especially in leads I, V^5 and V^6. Due to diminished contractility an angiocardiogram will show slow emptying of the left ventricle so that the aortic shadow may be poorly visualized.

In young infants symptoms due to left heart failure with acute pulmonary edema may be sudden in origin and are often precipitated by a minor infection. Death may occur suddenly or within a brief period of time. More frequently the infant may respond to treatment and survive the initial attack, but will suffer one or more recurrences until a final episode results in death some weeks or months later. An occasional infant may recover and be able to lead a normal life for years even though cardiomegaly and electrocardiographic abnormalities persist. In children in

whom symptoms are delayed past the age of two years there is a lesser degree of cardiac hypertrophy and endocardial thickening and the disease runs a more chronic course. The type of endocardial sclerosis associated with mural thrombosis which has recently been described in adults may have no relation to the developmental malformation, but may be of acquired origin. In the adults fibrotic endocardial changes have predominated although some increase in elastic tissue was present.

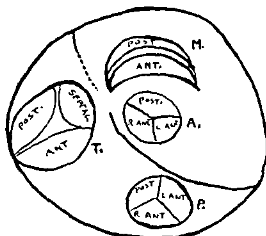


FIGURE 3 Diagram showing relation of the most frequent site of interventricular septal defect to the membranous space and to the valves of the heart. *P* denotes the pulmonic valve, *A*, the aortic, *M*, the mitral, and *T*, the tricuspid valves The dotted area in the interventricular septum denotes the membranous portion of the septum, the broken area, the site of septal defect Fibers of the bundle of His pass through the membranous space and the region posterior to the membrane. Heart block is unusual in association with the usual subaortic septal defect.

Various theories to explain the symptomatology of this lesion have been proposed. It has been suggested that the rigid endocardium may limit diastolic filling and systolic expulsion; that it may interfere with the proper conduction of contraction impulses and finally that it may interfere with the blood supply to the myocardium by preventing normal emptying of the thebesian veins into the ventricle.

Congenital Heart Block: Congenital heart block may be an independent malformation of the conduction system occurring in the absence of any associated cardiac anomaly.

Of the more than 100 cases reported in the literature prior to 1950 only fourteen cases with graphic proof of the diagnosis had come to necropsy. Six of these presented a normal ventricular septum. In one of these six individuals an ostium primum was present. Of the remaining cases one showed complete absence of the membranous septum while the others all presented multiple cardiac anomalies. In none was there found the uncomplicated subaortic septal defect in the usual anterior location. The bundle of His lies posterior to the usual high ventricular septal defect (Fig. 3). Embryologically, moreover, the development of the bundle of His

takes place prior to that of the ventricular septum. As a rule, even gross absence of the atrial or ventricular septum need not interfere with the preservation of conducting tissue. The bundle of His may be found in the rudimentary portion of a ventricular septum or in the posterior wall of a common ventricle.

The criteria for diagnosis of congenital heart block are the presence of a slow pulse noted early in life; graphic proof of the existence of heart block; and the absence of a history of infection, such as rheumatic fever or diphtheria, preceding the appearance of a slow pulse. The condition has been diagnosed *in utero* by the discovery of fetal bradycardia. It has occurred in siblings.

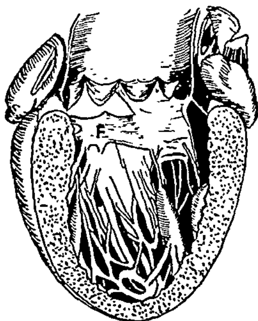


FIGURE 4. Subaortic stenosis. A band of fibrous tissue, *F*, encircles the wall of the left ventricle just below the aortic cusps (From Muir, D. C, and Brown, J W.: Brit. M. J. 1:966, 1935)

The idioventricular rate in childhood is faster than in adults. The rate can be accelerated during exercise or fever and following the administration of atropine or epinephrine. Slight slowing can be produced by ocular pressure. Variation in the intensity of the first sound may be present. An inconstant mid-diastolic sound or short murmur located to the right of the apex is not uncommon. A low-pitched parasternal systolic murmur is almost universally present and is indistinguishable from an innocent functional murmur. The presence of such a murmur has frequently been the only basis for the clinical diagnosis of ventricular septal defect. The heart usually seems top normal in size or slightly enlarged. In the absence of associated cardiac anomalies the contour is normal. It has been suggested that the auscultatory findings and cardiomegaly noted in patients with complete heart block may be related to the large stroke volume associated with the slow heart rate and the resultant large end diastolic

heart volume.[21] The prognosis varies with the presence and severity of associated abnormalities. When complete heart block is the sole anomaly, the condition may be asymptomatic and compatible with a long life[22] Stokes-Adams attacks have been reported in about 15 per cent of the cases, usually associated with severe cardiac defects. Their occurrence is serious, but when present in early life they have in isolated cases been known to disappear. Pregnancy seems to be well tolerated.

Congenital Aortic Stenosis:[23] This may involve the aortic valve or the subaortic region of the left ventricle. Subaortic stenosis may be due to muscular hypertrophy or more commonly to an annular fibrous thickening of the endocardium of the left ventricle located 1 to 2 centimeters below the valve, often involving the base of the anterior segment of the aortic valve. The posteromedial attachment may involve the ventricular aspect of the aortic leaflet of the mitral valve (Fig. 4). This rim of thickened tissue may become calcified in later life and serve as a site for the development of bacterial endocarditis. More rarely a diaphragm situated below the aortic valve blocks the egress of blood except through a small orifice. In valvular stenosis, surgical experience has disclosed the frequent presence of sclerotic formed cusps with thickened fused commissures. Poststenotic dilatation often develops beyond the site of stenosis. In subaortic stenosis, such dilatation may include the aortic valvular ring and sinuses of Valsalva. Valvular and subaortic stenosis usually occur separately but may be combined. Coarctation of the aorta, endothelial fibroelastosis, or patent ductus arteriosus may be associated with aortic stenosis. Cases have been reported of combined aortic and pulmonary stenosis and of concomitant ventricular septal defect.

Both valvular and subaortic stenosis may show varying degrees of severity and can rarely be differentiated clinically in life. Stenosis may be so slight as to remain asymptomatic or so severe as to result in congestive failure and death in infancy. It may increase in severity with time.

The condition may be suspected in the presence of a harsh systolic murmur and coarse thrill maximum in the first three intercostal spaces below the right clavicle transmitted to the suprasternal notch and the vessels of the neck. The murmur may be heard throughout the chest in children. In infancy it may resemble that of a ventricular septal defect and be heard best in the third and fourth intercostal spaces to the left of the sternum. The second aortic sound may be weak or absent but is often normal. When the stenosis is of significant degree, roentgenographic and electrocardiographic evidence of left ventricular hypertrophy may be noted. Marked cardiac enlargement, however, occurs only as a result of dilatation of the left ventricle due to failure or to associated aortic insufficiency. The ascending aorta may be dilated.

Although signs may be striking, symptoms are often absent for many years With severe stenosis, growth and development are retarded. There is a tendency to sudden death or to the early development of congestive failure. The presence of symptoms, such as fatigue, dyspnea or dizziness on exertion or syncopal attacks, indicates that stenosis is severe and compensation inadequate. The presence of weak peripheral arterial pulsations

associated with low pulse pressure and the appearance of progressive changes in the electrocardiogram with increasing inversion of T waves in the left precordial leads are also ominous findings.

Indirect tracings from the carotid artery will show anacrotic notching. Direct proof of the presence of aortic stenosis may be established by catheterization of the left side of the heart which will reveal a gradient in systolic pressure from ventricle to aorta. The absence of a pressure gradient with the patient under anesthesia may be misleading since the gradient depends not only on the size of the opening but also on the rate of flow. The flow increases during exercise but may be diminished when the patient is at rest under anesthesia.

Surgical procedures are now available to relieve aortic stenosis under direct vision with the aid of hypothermia or extracorporeal circulation. The operation does not restore the valve to normal and if it results in aortic insufficiency the individual may be in a worse state than before. Operation should be advised only after careful study and observation of the individual when signs of deterioration have begun to make their appearance.

Congenital Mitral Stenosis: This lesion is often associated with endothelial fibroelastosis and/or coarctation of the aorta. The mitral valve is greatly modified in appearance presenting nodular thickened rigid cusps fused to form a funnel-like orifice, sometimes associated with a perforated shelf or membrane at the base. The chordae tendineae are shortened and thickened. An hypertrophied, dilated, left atrium is frequently associated Depending on the presence or absence of associated anomalies, such as coarctation or aortic stenosis, the left ventricle in reported cases has been large, normal, or small. Of fourteen necropsied cases reported in the literature, a presystolic or diastolic apical murmur was described in five and only a systolic murmur in five. All but one of these individuals died of congestive failure at a relatively early age (sixteen months to three years). The author has seen four children with coarctation who presented the typical presystolic murmur of mitral stenosis. The coarctation was successfully resected in all of these children by Dr. Julian Johnson. Since the possibility of performing a successful valvotomy on congenitally stenotic valves seemed slim, it was deemed advisable to defer operation on the mitral valve as long as these children remained symptom-free. Three cases of valvotomy for congenital mitral stenosis have been reported.[24]

Pulmonary Stenosis with Intact Ventricular Septum and Closed Foramen Ovale (Pure Pulmonary Stenosis): In the majority of cases the site of stenosis is at the pulmonary valve. Commonly the leaflets of the valve are fused to form a dome-shaped structure with a small central aperture. Less frequently the cusps are thickened and deformed creating a slit-shaped opening. In a minority of cases the site of stenosis may be at the upper, mid or lower portion of the infundibulum. Valvular and infundibular stenosis may be combined. The pulmonary artery is frequently dilated beyond the site of stenosis. As a result of the stenosis the work of the right ventricle increases and the systolic pressure within the ventricle rises. The pulmonary flow is equal to the systemic flow as long

as the right ventricle by increased work and rise in pressure can provide an adequate output against the resistance of the stenotic pulmonary valve.

Cyanosis is not present when the atrial septum is intact. With mild or moderate degrees of stenosis the individual may be asymptomatic well into adult life. In the presence of marked stenosis fatigue and dyspnea on exertion may make their appearance in early life increasing progressively with age. Bacterial endocarditis is an occasional complication. Death not uncommonly is due to congestive failure.

Physical examination reveals a systolic thrill in the pulmonary area; a single or narrowly reduplicated second pulmonic sound often of diminished intensity; a systolic murmur maximum over the pulmonary area frequently heard over the entire chest. Enlargement of the right atrium and right ventricle will be noted on the *roentgenogram*. There may be disproportionate enlargement of the main and left pulmonary artery as compared with the right pulmonary artery with normal or diminished vascularity in the peripheral lung fields. The *electrocardiogram* may range from normal to one showing a severe degree of right ventricular preponderance depending on the severity and duration of stenosis. High P waves are common. In severe cases S-T depression and inverted T waves may be present in leads 2 and 3 and in the precordial leads. Polycythemia is absent; the oxygen saturation is normal; the circulation time is normal unless congestive failure is present when it may be prolonged. *Catheterization* will reveal increased systolic pressure in the right ventricle which may exceed systemic pressure. Pressure tracings from the right ventricle show curves with a peaked symmetrical appearance (Fig. 2). The systolic pressure in the pulmonary artery will be low. The site of stenosis may be determined by noting the pressure changes as the catheter is withdrawn from the pulmonary artery into the right ventricle. In valvular stenosis there is an abrupt change of pressure at the valve whereas in infundibular stenosis there is a transitional zone of intermediate pressure as the catheter passes through the infundibular chamber. Selective *angiocardiography* with the tip of the catheter in the outflow tract of the right ventricle may provide good visualization of the stenotic site

Valvotomy or infundibulotomy will relieve the strain on the right ventricle. The creation of a shunt between the systemic and pulmonary circulation is of no value since the arterial blood is fully saturated and the volume of pulmonary blood is adequate. Operation is not indicated in the asymptomatic individual with only slight hypertension in the right ventricle. It should be recommended in the individual with marked or progressive cardiac enlargement, increasing symptoms, progressive changes in the electrocardiogram, or a systolic pressure in the right ventricle greater than 100 mm. of mercury.

Lesions of Arteriovenous Shunt

Persistent Patency of the Ductus Arteriosus:[25] The ductus arteriosus may persist as a short canal or rarely as a direct orifice between the right wall of the descending arch of the aorta and the pulmonary artery or its left branch. The diameter of the lumen may vary from the size of a fine

probe or bristle to 1 cm. or more. The ductus is often of wide diameter at its aortic end where it may appear at the bottom of a tent-shaped depression. Atherosclerosis or calcification of the walls of the ductus and pulmonary artery may predispose to the formation of thrombi or to rupture of these vessels. The primary shunt of blood from the aorta into the pulmonary artery results in enlargement of the pulmonary artery and its branches varying in degree with the size of the lumen and the extent of the shunt. It has been estimated that the leak from the aorta in the majority of patients is from 20 to 40 per cent, although in severe cases it has ranged up to 70 per cent. The output of the left ventricle exceeds that of the right ventricle by the amount which enters the ductus. In most instances the lungs accommodate themselves to the increased

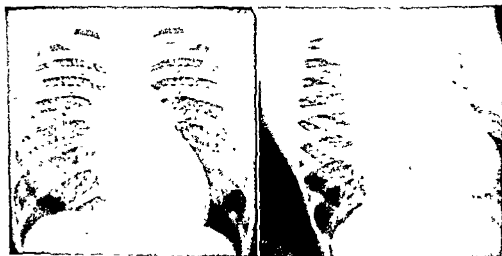


FIGURE 5. Roentgenograms from thirteen-year-old girl with patent ductus arteriosus (diagnosis confirmed by operation) Slight enlargement of pulmonary segment in A-P and right oblique view; cardiac contour otherwise within normal limits

pulmonary blood flow without significant increase in pressure. If the ductus is wide and short, however, a large volume of blood is shunted into the lungs under systemic pressure. As a result there may be postnatal persistence of the medial hypertrophy which occurs normally in the pulmonary arterioles of the fetus. Arteriolar resistance and pulmonary pressure remain high and the work of the right ventricle increases.

The lesion occurs most frequently in females. Except for an occasional infant who develops congestive failure there are often no symptoms in childhood. Cyanosis is not present if normal pressure relations in the aorta and pulmonary artery prevail. If the shunt is large there may be interference with growth and development because of the decreased blood supply to the periphery. Tachypnea or dyspnea on exertion may be a prominent symptom. A frequent complication is the development of bacterial endarteritis appearing first around the margins of the pulmonary end of the ductus or on the opposite wall of the pulmonary artery but

ultimately involving the aortic orifice and leading to the formation of vegetations within the heart itself. Death may be due to cardiac failure: usually left ventricular in infancy, often right ventricular in later life.

A systolic thrill may be felt to the left of the upper sternum in seventy per cent. The second pulmonic sound is accentuated unless obscured by the murmur. The pathognomonic finding is a continuous murmur below the left clavicle which begins at various intervals after the first sound, attains its maximum intensity late in systole and early in diastole after which it fades away. Varying degrees of intensity and of transmission may occur ranging from a soft continuous humming blow localized to a small area within a single interspace to a loud, thundering "machinery" murmur audible over four or more interspaces. The systolic component may



FIGURE 6 Patent ductus arteriosus. Roentgenograms from nine-year-old girl with precordial bulge, coarse parasternal systolic thrill, thundering continuous murmur below left clavicle, systolic murmur elsewhere over chest, wide pulse pressure, normal ECG. Marked cardiac enlargement to left and downward in A-P view with prominence in pulmonic region and enlarged hilar shadows. Lateral view shows enlargement anteriorly (right ventricle) and posteriorly (left ventricle) Ligation of large patent ductus at the age of sixteen years by Dr. Julian Johnson resulted in return of cardiac size to normal (see Fig 8) with disappearance of thrill and murmurs

be heard with lessened intensity over the precordial region and occasionally over the entire chest as well as in the carotid and axillary arteries. A mid-diastolic blow is often present to the right of the apex when the heart is large. If the shunt is sufficiently great the fall in diastolic level of blood pressure will result in increased pulse pressure with capillary and Corrigan pulse.

Roentgenogram: (Figs. 5, 6, 9) If the shunt is small the heart is of normal size and contour even though a continuous murmur is present. In a review of the roentgenograms of 124 children with uncomplicated patent ductus proven by operation the heart was within normal limits of size in 32 per cent, slightly or moderately enlarged in 36 per cent, greatly

enlarged in 32 per cent.[25] The left ventricle was involved in all hearts in which cardiac enlargement was present. Enlargement of the left atrium was noted in 20 per cent of the group and in 50 per cent of the greatly enlarged hearts. Only in hearts of great size could enlargement of the right atrium and right ventricle be recognized. The pulmonary segment was prominent in 70 per cent; associated with increased vascularity of the lung fields in 60 per cent.

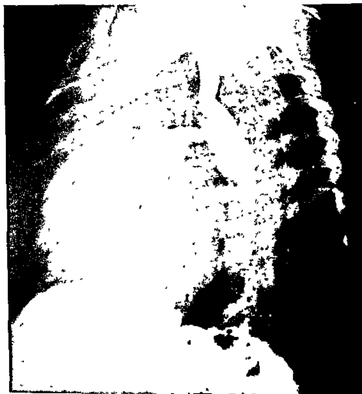


FIGURE 7 Patent ductus arteriosus *Aortogram* from three-year-old boy who presented a systolic murmur over the entire chest maximum third interspace left of sternum with no diastolic component, marked cardiac enlargement, enlarged pulmonary artery and branches Passage of contrast medium from the aorta into the pulmonary artery is visualized At operation a large ductus was severed by Dr Earl Wrenn

The *electrocardiogram* is within normal limits or shows some evidence of left ventricular enlargement in precordial leads. A high R and small S in leads to the right of the precordium may be noted in the infant or small child. Prolongation of P-R and delayed ventricular activation in V^1 suggestive of right bundle branch block occurs rarely. Broad notched P waves; diphasic or inverted T waves may be noted occasionally in individuals with definite cardiac enlargement.

Catheterization of the heart reveals a content of oxygen in the blood from the pulmonary artery significantly greater than that in the right ventricle. Pressure in the right ventricle and pulmonary artery may be normal or increased. It may be possible to pass the catheter from the pulmonary artery through the ductus into the descending aorta.

Angiocardiography: Various indirect signs have been described which may lead one to suspect the presence of a patent ductus. Except for early visualization of the descending aorta in the presence of a reverse ductus, angiocardiography however is less satisfactory than aortography. *Aortograms* will demonstrate the passage of contrast medium from the aorta into the pulmonary artery through the ductus (Fig. 7).

The continuous murmur of a patent ductus is heard only when the pressure in the aorta is higher than the pressure in the pulmonary artery both in systole and in diastole. In the presence of pulmonary hypertension shunting of blood may occur only during systole and only a systolic murmur may be heard. In rare cases no murmur may be heard presumably because of balanced pressure in the great vessels. During fetal life the pressure in the pulmonary artery is relatively high while the pressure in the aorta is low. With expansion of the lungs and disappearance of medial hypertrophy in the intrapulmonary arterioles pulmonary resistance falls At birth and for a varying period subsequently no murmur or only a systolic murmur may be associated with a patent ductus. As the aortic pressure increases and the pulmonary pressure decreases the diastolic component makes its appearance. Later in life the continuous murmur may disappear with the appearance of pulmonary hypertension or during congestive failure. It may never be present if for any reason fetal pulmonary hypertension persists into postnatal life.

The following case report is of interest since it exemplifies the possibility of death in early youth due to heart failure and also provides an example of the disappearance of a continuous murmur during congestive failure:

Case Report. Patent ductus arteriosus, intracardiac mural thrombi; recent small hemorrhagic infarct of lung. Death due to cardiac failure.

F, fourteen years. First seen at the age of six years by Dr. F. C Wood in April, 1933, at the Children's Cardiac Clinic of the Hospital of the University of Pennsylvania The heart was enlarged and presented a rough, pulmonic systolic thrill; a to and fro machinery murmur in the second left intercostal space, a rough systolic murmur in the third intercostal space and a softer systolic murmur at the apex The electrocardiogram was normal A diagnosis of patent ductus arteriosus was made

On her last visit to the clinic in February, 1939, a loud machinery murmur and coarse continuous thrill were present in the pulmonary area A systolic murmur was audible over the lower precordium, also over the left carotid and left axillary arteries The second pulmonic sound was obscured by the machinery murmur. Blood pressure was 100/60 She was lost sight of until March, 1940, when the writer chanced to meet her in one of the public high schools She had been attending school regularly and in the absence of symptoms had decided that attendance at the clinic was unnecessary *A thundering machinery murmur was still present.*

Two months later she was admitted to the University Hospital on the service of Dr O. H P Pepper One week prior to admission she had fainted while leaving church During the succeeding week she suffered from weakness and anorexia On admission the patient was markedly pale but did not appear uncomfortable The apex beat was situated at the anterior axillary line. *A rough*

systolic murmur and systolic thrill were present in the pulmonic area; no other murmur could be detected. The second pulmonic sound was accentuated. The liver was not felt. Three days later her condition suddenly became critical with the development of severe abdominal pain, cyanosis, and marked enlargement and tenderness of the liver. An electrocardiogram taken at this time was interpreted as showing occasional 2:1 right bundle branch block. She died on the following day of acute right-sided heart failure. Some hours prior to her death she was seen by Dr. Wood who, seven years before, had made the first notation concerning her machinery murmur. He commented on the *absence of murmurs at this final examination.* Necropsy performed by Dr Sheldon revealed about 100 cc. clear fluid in the pericardial cavity; 200 cc. in each pleural cavity, and 400 cc. in the peritoneal cavity. The liver was enlarged 6 cm. below the costal margin. Heart weight: 460 Gm. All chambers were dilated, especially the left ventricle. The mitral valve was somewhat thickened with small pale nodules along the free margin. Loosely attached thrombi were present in the columnae carnae of the left ventricle. The tip of the right auricula was filled with a clot firmly attached to the wall. The foramen ovale was closed. The circumference of the aortic valve was 5 cm.; the pulmonic, 6 cm.; the mitral, 10.5 cm and the tricuspid, 13 cm The left ventricular wall was 0.9 to 1.2 cm. thick, the right ventricle, 0 3 cm A 3 mm. patent ductus was present. About a dozen pinhead-sized nodules were attached to the thickened edges of the ductus The aorta was small Microscopically the mitral valve showed irregular thickening but no exudate. The immediate cause of the terminal cardiac failure remained obscure, clinically and pathologically.

The value of closure of a patent ductus by ligation or division has been proven in thousands of cases. Symptoms disappear and the heart returns to normal size following successful operation in early life (Fig. 8). The death rate in 3433 operations in fifteen surgical centers in the United States was 1.9 per cent.[26] Since the closure of a patent ductus is an extracardiac procedure relatively free from risk it should be recommended for all children provided an anesthetist experienced in the use of intratracheal anesthesia in childhood and a skilled vascular surgeon are available. If the diagnosis can be made within the first year the operation may be performed at that time. If not it is wise to wait until the negativistic period is past (at about four years) so that the child may go through the procedure with minimum psychologic trauma. Because of advancing sclerosis and calcification the hazard of hemorrhage increases with age.

Successful ligation in the presence of bacterial vegetations has been performed, with cure due to surgery alone in 61 per cent of thirty-three reported operations. Ligation for the treatment of bacterial endarteritis is of value only if bacterial vegetations are confined to the ductus. It cannot be expected to influence vegetations which have invaded the heart itself. At this early stage penicillin or other antibiotics administered in sufficiently large doses would probably produce equally good results without running the risk of rupture of the friable inflamed ductus through operative intervention. Ligation in the presence of bacterial infection should probably be reserved for infections due to organisms resistant to

the known antibiotics or for individuals with heart failure. After recovery, closure of the ductus would be advisable.

A noncyanotic individual with typical continuous murmur, normal electrocardiogram or one which shows evidence of left ventricular hypertrophy, normal or increased vascularity in the lung fields may be referred for operation without further studies. The existence of a septal defect or mitral disease would be no contraindication to closure of the ductus. If coarctation is present the major procedure would be resection of the con-

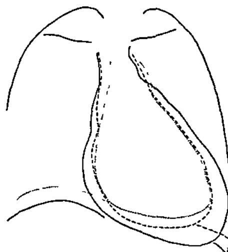


FIGURE 8 Decrease in size of heart following ligation of ductus arteriosus Solid line 7/5/40 (twelve days before operation), cardiac area 71 per cent above predicted normal; broken line 10/1/40, cardiac area 29 per cent above predicted normal; dotted line 5/25/43, cardiac area at upper normal limits Note elevation of diaphragm with decrease in size of heart (see Fig 6).

stricted segment in the aorta, division of the ductus being performed incidentally. Operation is contraindicated in the presence of lesions such as pulmonary atresia for which patency of the ductus is compensatory. Such lesions would be associated with anoxemia, inadequate pulmonary circulation and evidence of right ventricular preponderance in the electrocardiogram.

In the infant with no murmur or a systolic murmur and congestive failure in whom the presence of a patent ductus is suspected aortography is the best procedure to establish the diagnosis (Fig. 7). In the older individual cardiac catheterization is more valuable since it will supply information as to the degree of hypertension and extent of pulmonary flow (Fig. 9). Closure of a ductus in the presence of pulmonary hypertension with high diastolic pressure can sometimes be performed safely in the child whereas it would be a hazardous procedure in the adult. In the adult progressive and irreversible intimal fibrosis may have increased the pulmonary resistance to such a degree as to make the patent ductus an essential safety valve to the right heart.

Differential Diagnosis: Errors in diagnosis may result from the presence of a continuous murmur arising from sources other than a patent ductus.

The normal *venous hum* is often mistaken for the murmur of a patent ductus. The venous hum as a rule is heard only in the erect position, below the right clavicle or over the manubrium, and is accentuated by extension of the neck or by turning the head to the opposite side. The murmur of a patent ductus is heard best below the left clavicle in the recumbent position and is not influenced by movement of the head. Continuous murmurs due to *arteriovenous fistulas* of the thoracic wall or of the coronary arteries have been mistaken for murmurs arising from a patent

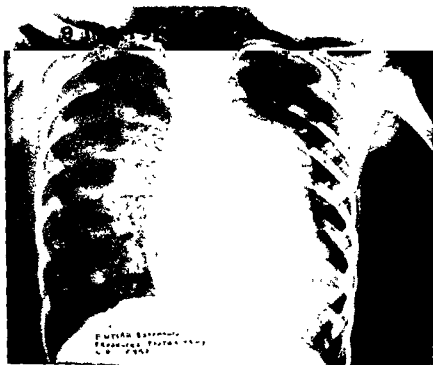


Figure 9. Patent ductus arteriosus. [illegible] -year-old girl [illegible] posterior left [illegible] standard limb [illegible] hilar vascular shadows, biventricular enlargement. *Catheterization* showed oxygen content of blood in right ventricle to be 12.0 vol. per cent and in main pulmonary artery 14.7, mean pressure in right ventricle 40 mm. Hg and in pulmonary artery 66 mm. Ligation of large ductus by Dr. Julian Johnson was followed by disappearance of murmurs. Heart of normal size six years after operation, but pulmonary artery still large.

ductus. *Ruptured sinus of Valsalva* and *ventricular septal defect with deformed aortic valve* leading to aortic insufficiency each present some clinical features similar to those noted with a patent ductus. Rarely a soft continuous murmur may be heard below the left clavicle in infants with total anomalous pulmonary venous drainage into a left vertical vein. The lesion that is most difficult to differentiate is an *aortic septal defect*.

An *aortic septal defect* (aortic window)[27] consists of a localized communication between the aorta and pulmonary artery situated just above the semilunar valves. The physiologic effect is similar to that produced by

a patent ductus. As a result the diagnosis has only rarely been made in advance of operation for a suspected patent ductus. Pulmonary hypertension is frequently present. In such cases a systolic murmur or no murmur may be noted rather than a continuous murmur. Fluoroscopic examination may reveal marked dilatation and increased pulsation of the ascending aorta. A retrograde arteriogram will show opacification of the main pulmonary artery. A catheter passed through the defect would move up the arch of the aorta instead of down the descending aorta.

If a venoarterial shunt is present the differentiation of patent ductus and aortic window could be made by angiocardiography. A septal defect would show simultaneous filling of the ascending aorta and pulmonary artery. A patent ductus with reverse flow would show early opacification of the descending aorta from the pulmonary artery, with later filling of the ascending aorta when the contrast medium had passed through the left ventricle. In a patient with reverse ductus the arterial oxygen saturation in the right arm would be normal as compared with decreased oxygen saturation in the lower extremities, whereas the oxygen saturation would be low in all four extremities in an individual with an aortic window.

In a few isolated cases an aortic septal defect has been closed surgically, but the procedure is technically difficult because of the location of the defect behind the pulmonary trunk in close approximation to the aortic valve and to the origin of the coronary arteries.

Defects of the Ventricular Septum:[28] Localized defects resulting from failure of the bulbar septum to descend to meet the ventricular septum usually lie at the base in relation to the anterior part of the membranous septum and open into the sinus of the right ventricle behind the septal cusp of the tricuspid valve or rarely into the floor of the right atrium. Less frequently, the defect lies in the extreme anterior part of the septum and opens into the conus of the right ventricle just below the pulmonary valve. Rarely, one or more perforations may be situated in the lower part of the muscular septum.

The lesion frequently runs a symptomless course, consistent with a long and healthy life. In extreme contrast are the infants with large defects who die of congestive failure associated with pulmonary emphysema and recurrent pulmonary edema. In the absence of complications such as pneumonia, heart failure, or pulmonary hypertension there is no cyanosis. Occasionally the defect may involve the septal cusp of the aortic valve or the median cusp of the tricuspid valve which remains rudimentary or becomes adherent to the septum (Fig. 3). The resultant regurgitation may lead to early cardiac failure. The major complication is the development of bacterial endocarditis about the edges of the defect or on the fibrous patch on the opposite wall of the right ventricle which results from the force of the stream shunted through the defect.

Cardiac enlargement is variable, depending on the size of the orifice and the degree of the shunt. A systolic thrill may be present to the left of the sternum at the level of the third and fourth intercostal spaces, accompanied by a prolonged systolic murmur with maximum intensity at this same area, frequently transmitted to the apex, sometimes present in the

left interscapular region or over the entire chest. The second pulmonic sound is normal or moderately accentuated. The cardiac contour is normal or may show varying degrees of enlargement of both the right and left ventricles, best observed in the left anterior oblique position. An enlarged pulmonic arc is not common unless the shunt is very large or enters the right ventricle directly below the pulmonic valve. In the uncomplicated case the *electrocardiogram* is normal or may show evidence of biventricular enlargement in the precordial leads. In the presence of heart failure and marked cardiac enlargement inversion of T waves and prolongation of P-R may be noted. The pattern of right ventricular preponderance may appear in association with marked pulmonary hypertension. The clinical association between ventricular septal defect and congenital heart block is frequently reported, but has not been substantiated by necropsy findings. *Catheterization* reveals an oxygen content in the blood of the right ventricle significantly higher than in the right atrium. Pressure readings in the right ventricle and pulmonary artery may be normal or elevated depending on the presence of changes in the arterioles of the lung leading to increased resistance and pulmonary hypertension.

An improved understanding of the hemodynamics of this lesion has been developed in recent years by Seltzer.[28a] A ventricular septal defect creates a situation in which the left ventricle can pump blood through two outlets —the aorta and the defect. Since the normal pressure in the right ventricle is relatively low, the right ventricle provides an outlet of low resistance through which the major volume of blood might flow. A small orifice would create sufficient resistance to limit the flow through the defect. Seltzer estimates that in the adult defects smaller than 1.5 cm. in diameter are consistent with normal pressure relations between the two ventricles, and the maintenance of an adequate systemic blood flow even though the pulmonary blood flow may be greater in volume than the systemic flow. With larger defects, however, a disproportionate amount of blood would be ejected into the right ventricle under systemic pressure. To maintain an adequate systemic circulation the resistance in the lungs must be increased. This is accomplished by persistence of the medial hypertrophy in the pulmonary arterioles which is normal in the fetus. The systolic pressure in the two ventricles becomes equalized. The shunt may be predominantly left to right; or bidirectional. Due to progressive fibrotic thickening of the intima, pulmonary pressure continues to increase Ultimately the shunt becomes predominantly right to left with the appearance of anoxemia and cyanosis. Since the upper portion of the ventricular septum anatomically runs a spiral course the aortic root may come in contact with both ventricles when the anterior part of the membranous septum is absent. Such a condition morphologically and functionally resembles the Eisenmenger complex in which an anatomically dextroposed aorta overrides a ventricular septal defect.

Due to the close relation of the usual subaortic defect to valve leaflets satisfactory closure of the defect can be performed only under direct vision with the aid of extracorporeal circulation. Such operations are now being performed successfully.

Ventricular Septal Defect and Pulmonary Stenosis.[36] These may be combined and may occur in association with an arteriovenous shunt. The degree of pulmonary stenosis, which may be valvular, infundibular or both, is not great. The pressure in the right ventricle is increased, but the pressure in the pulmonary artery may be normal or moderately elevated. This syndrome is sometimes called an "acyanotic" tetralogy of Fallot.

In association with a very large arteriovenous flow through an atrial or ventricular septal defect a gradient ranging from 10 to 40 mm. of Hg, presumably due to the Venturi mechanism, may be present between the right ventricle and a normal pulmonary valve.

Defects of the Atrial Septum:[29] Probe patency of the foramen ovale exists in some 20 per cent of normal hearts and should not be considered abnormal. Under conditions which raise the pressure in the right atrium such an anatomically open but functionally closed foramen may become patent and blood and emboli be transmitted into the left atrium, whereas increased pressure in the left atrium favors closure due to a valve-like action of the foramen ovale. An anomalous atrial septal defect may be situated above the foramen ovale in the upper posterior portion of the septum (sinus venosus defect) in which case the right pulmonary veins may be displaced into the right atrium; or below the foramen ovale in the lower part of the septum (persistent ostium primum) with the upper margin formed by the lower free border of the atrial septum, in which event associated cleavage of the anterior segment of the mitral valve may produce a congenital mitral insufficiency. Most frequently the defect is due to congenital absence of all or part of the valve of the foramen (persistent ostium secundum). Defects may be single or multiple and of varying size.

Although the pressure differential between the atria is small the size of the defect may be sufficiently great to permit a large flow of blood into the right atrium. The right atrium, right ventricle, pulmonary artery and its branches become enlarged. Sclerotic and atheromatous changes may develop in the walls of the pulmonary vessels Although the excess blood is returned to the left atrium it is again shunted through the defect into the right atrium The left atrium, left ventricle and aorta remain relatively small. The pulmonary flow is greater than normal but the systemic flow remains within normal range. Over the course of years intimal fibrosis may develop within the pulmonary arterioles increasing the resistance sufficiently to produce pulmonary hypertension. In such cases there may be a reversal of flow from right to left with the appearance of anoxemia and cyanosis.

The lesion occurs most frequently in females. The defect may present no clinical signs and be unrecognized in life. Cyanosis is not present in the absence of heart failure or pulmonary hypertension sufficiently great to produce a reversal of flow through the defect. Signs of diminished flow through the aorta—slight build, frail health, low blood pressure, and small radial pulse—may be present if the shunt is sufficiently great. The capacity for exercise is often good; repeated pregnancies and surgical operations have been well borne. In the past, superimposed rheumatic infection has

been a frequent complication, usually resulting in mitral stenosis often with atrial fibrillation, but other valves may be attacked and adhesive pericarditis may be associated. The combination of atrial septal defect and mitral stenosis (Lutembacher syndrome) leads to the most extreme degree of enlargement of the right side of the heart. Bacterial endocarditis is rare. Thrombosis of the pulmonary artery with embolic lesions of the lung may develop on the basis of sclerotic changes in the vessel wall. The most frequent cause of death is congestive heart failure, typically right ventricular

With lesions of sufficient size left-sided chest deformity may result from the marked cardiac enlargement. The second pulmonic sound is accentuated and widely split. Although murmurs are frequently present, it is questionable whether they are ever due to the lesion itself. A faint systolic thrill and low pitched systolic murmur noted over the pulmonic area are probably due to dilatation of the pulmonary artery with relative stenosis of the less distended pulmonary ring. In older individuals a diastolic murmur along the left side of the sternum due to relative pulmonary insufficiency may appear. A mid-diastolic blow or third heart sound may be heard to the left of the lower sternum. Defects at the lower part of the septum associated with extensive deformities of the atrioventricular valves may give rise to a systolic murmur best heard at the apex or tricuspid area. When mitral stenosis is present, the characteristic diastolic rumble may be heard to the right of the apex. The *roentgenographic contour* may be normal if the shunt is small. If the shunt is sufficiently great there will be evidence of dilatation of the right side of the heart. In infancy, the heart may present a globular shadow in mid-position due to the primary dilatation of the right atrium. In later life, the characteristic features in the anteroposterior view are enlargement of the cardiac shadow, more pronounced to the left although due to enlargement of the right ventricle; a small aortic knob; prominent rounded pulmonic arc, enlarged, pulsating hilar shadows, contrasting with the clear lung fields (Fig. 10). In the right anterior oblique position there is no enlargement of the left atrium unless mitral stenosis is present. In the left anterior oblique position the aortic window is obscured by the enlarged left branch of the pulmonary artery and the anterior surface of the heart shows increased saliency. In a minority of cases with terminal failure, instead of the typical configuration the heart presents a large globular shadow resembling that due to pericardial effusion or extreme acute cardiac dilatation.

The *electrocardiogram* may be normal if the defect is small. With large defects and definite cardiac enlargement there may be right axis deviation; evidence of right ventricular enlargement in precordial leads; prolonged P-R; delayed conduction within the right ventricle ranging from simple notching to bundle branch block; and depressed ST and inversion of T waves in Leads II and III. Atrial fibrillation is a late finding in rheumatic hearts or in the older individual.

With ostium primum and deformity of the atrioventricular valves the electrocardiogram as well as the murmur differs from that noted with atrial defects not associated with valvular deformity. Standard limb leads show prominent S waves and left axis deviation whereas precordial

leads show features characteristic of biventricular enlargement. The clinical picture resembles that seen with common atrioventricular canal rather than with a simple atrial defect.

Angiocardiography may demonstrate the extreme enlargement of the right heart and pulmonary artery and the presence of a small aorta. With a large defect there may be continuous visualization of all chambers and the pulmonary artery when the left heart has become opacified due to the left to right shunt through the atrial defect. *Catheterization* will reveal *an oxygen content of blood in the right atrium significantly higher than* in the vena cava. Definitive proof of the diagnosis is obtained if in addition the catheter is passed directly through the defect into the left atrium where arterial blood may be obtained.

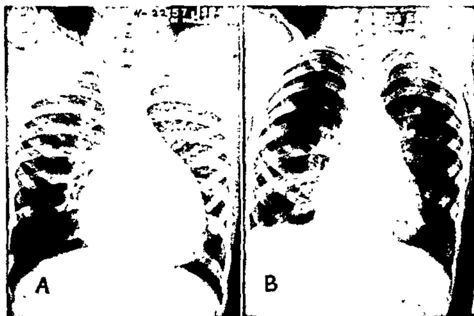


FIGURE 10. Decrease in cardiac size following closure of an atrial septal defect in a ten-year-old girl A, Roentgenogram taken on day preceding operation Note cardiac enlargement and prominent pulmonary vascular shadows B, Two weeks after closure of atrial defect (From Ash, R, Johnson, J., Koop, C E, Friedman, S, and Rashkind, W: Cardiovascular Surgery in a Children's Hospital. I. Acyanotic Lesions A Review of 241 Operations J Pediat 54.133, 1959)

Closure of atrial septal defects under direct vision with the aid of hypothermia and circulatory stasis or of extracorporeal circulation is now being performed successfully. The risk is minimal when the lesion is situated in the region of the foramen secundum.[32] Disappearance of the murmur and decrease in the size of the heart may occur rapidly Since endocarditis rarely develops, closure of an atrial septal defect is essential only when it is advisable to reduce the work of the heart. Small defects need not be closed. Operation should be advised when there is electrocardiographic and roentgenographic evidence of enlargement of the right side of

the heart together with a pulmonary flow at least twice the systemic flow. Operation is contraindicated in the presence of pulmonary hypertension with high diastolic pressure when the pulmonary blood flow has become normal or only slightly increased. In the presence of such a degree of pulmonary hypertension, the atrial defect functions as a safety valve to the right side of the heart.

Closure of defects situated near the atrioventricular valves (ostium primum) carries a higher operative risk and should be performed only with the aid of extracorporeal circulation.

Partial Anomalous Pulmonary Venous Connection (Partial Transposition of Pulmonary Veins): One or more of the right pulmonary veins drain into the right atrium either directly or via the superior or inferior vena cava. An atrial septal defect is frequently present. When the veins drain into the superior vena cava the septal defect is usually situated above the foramen ovale in the region of the primitive sinus venosus. When the anomalous vessel drains into the inferior vena cava a bandlike vascular shadow, parallel or posterior to the right side of the heart, which disappears in the region of the right cardiodiaphragmatic angle may be visible in the conventional roentgenogram.[30] Additional anomalies of bronchial distribution and accessory pulmonary arteries from the descending aorta may be present.[31]

The clinical picture and catheterization findings often cannot be distinguished from those due to an uncomplicated atrial septal defect since a rise of oxygen content at the atrial level is present in both conditions. Occasionally a systolic murmur may be louder in the right side of the chest than in the left. High arterialization of blood obtained from a vena cava during cardiac catheterization should lead one to suspect the presence of a transposed pulmonary vein. The diagnosis may be established by the passage of a catheter from a vena cava or right atrium into the aberrant vessel or by means of indicator dilution curves obtained following injection of dye into the right or left pulmonary artery. Selective angiocardiography with introduction of contrast substance directly into a branch of the pulmonary artery should opacify the aberrant pulmonary veins and the right atrium in rapid sequence.

If less than half the volume of blood from the lungs enters the right atrium through transposed pulmonary veins, a normal duration of life is possible. Ready fatigue, delayed growth and poor nutrition may be noted in childhood, however, and death due to right-sided congestive failure has been reported in adult life.

The orifice of anomalously connected right pulmonary veins may be transposed into the left atrium by attaching the anterior edge of the associated atrial septal defect anteriorly and to the right of the anomalous veins, thus closing the defect simultaneously. When the right pulmonary veins enter the superior vena cava at some distance above the heart it is possible to use a purse-string type of suture so as to cause the pulmonary veins to enter the left atrium and the superior vena cava to enter the right atrium.[32]

A ventricular septal defect which opens into the right atrium or which

is associated with tricuspid regurgitation may present catheterization findings similar to those of an atrial septal defect or partial transposition of the pulmonary veins. A triatrial heart with atrial septal defect will also present an arterial shunt at the atrial level, but the latter lesion will be associated with increased pulmonary capillary (wedge) pressure as well as pulmonary hypertension.

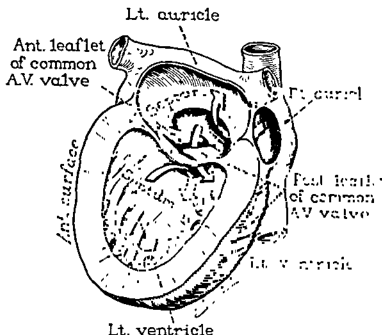


FIGURE 11. Common atrioventricular canal. The lateral walls of the left atrium and ventricle have been removed. The atrioventricular canal is common to both

Common Atrioventricular Canal:[33] This lesion is due to arrest of development of the primitive anterior and posterior atrioventricular endocardial cushions which results in failure of fusion of the atrial and ventricular septa and deformities of the atrioventricular valves of varying degree. A persistent ostium primum with cleft mitral and/or tricuspid valves represents the simplest form of this anomaly and has been termed "partial common atrioventricular canal."

The complete lesion consists of a common canal connecting the atria and ventricles A persistent ostium primum is combined with a defect in the upper portion of the ventricular septum. There is thus at this region free communication between the four chambers of the heart. The common orifice is usually surrounded by four or five cusps including one large anterior cusp and one large posterior cusp with two or three small lateral cusps (Fig. 11). The frequency of mongolism in association with this lesion was pointed out by Abbott.

Of twelve infants seen by the writer with complete common atrioventricular canal proved by necropsy, nine were Mongols. All showed poor nutrition, delayed development, cardiomegaly, and respiratory distress. None showed definite cyanosis except terminally, although there was a tendency to a peculiar grayish color on crying. All had died before the age of two years, only three having survived the first year. No murmur was noted in three; the others presented precordial systolic blows best heard to the left of the sternum either at the base or lower sternal region; occasionally transmitted into the axilla, but never heard well posteriorly. Peripheral pulsations tended to be weak. *Roentgenograms* showed enlargement of the cardiac shadow to the right of the sternum in the anteroposterior view, with posterior projection beyond the spine in the left anterior oblique view. Pulmonary vascular shadows were increased. The superior mediastinal shadow may be narrow. The electrocardiogram (taken in six cases with precordial leads in four) showed left axis deviation and prominent S waves in the standard limb leads with a QRS pattern in the precordial leads suggestive of the presence of biventricular enlargement associated with delayed activation of the right ventricle.

A ten-year-old girl who presented a complete common atrioventricular canal at necropsy had been followed for eight years. During this period she developed increasing cyanosis and dyspnea. She began to squat at five years and finally sat constantly in a squatting position. She was subject to attacks of paroxysmal tachycardia. Her death was due mainly to anoxia caused by diminution in blood flow resulting from progressively increasing pulmonary vascular resistance as well as by the venous arterial shunt secondary to pulmonary hypertension. The diagnosis had been made in life because of the characteristic electrocardiogram and the presence of a thrill in the lower precordial region associated with a high pitched systolic blow at the apex.

Partial common atrioventricular canal can be corrected surgically under direct vision with the use of extracorporeal circulation. The risk although greater than that associated with closure of an ostium secundum defect is not prohibitive. A prothesis is used as a rule in the closure of the ostium primum. The clefts in the atrioventricular valves may be sutured together. Surgical correction of the complete form of common atrioventricular canal is more difficult and associated with a high mortality rate.

Triatrial Heart:[34] A diaphragm divides the left atrium into an upper posterior and lower anterior portion. The pulmonary veins enter the small cavity at the right upper part of the left atrium. The atrial appendage leads from the main anterior chamber. The anomalous septum usually carries an opening through which the blood passes from the right upper cavity into the lower part of the left atrium and thence to the mitral orifice. The effect on the circulation is comparable to that which occurs with mitral stenosis.

Approximately half the patients die in infancy. An infant with this anomaly who died at the Children's Hospital of Philadelphia at six weeks had suffered recurrent attacks of dyspnea and cyanosis beginning at three weeks usually induced by crying and exertion. No murmur or thrill was

noted. There was marked hepatomegaly. The roentgenogram showed fulness of the pulmonary segment and right ventricular enlargement. At necropsy an accessory atrial chamber was found receiving all pulmonary veins. The right side of the chamber communicated with the right atrium through a foramen one cm. in diameter. The left side was separated incompletely from a small left atrial cavity by a sickle-shaped fold. The left ventricle was small; the right atrium and right ventricle extremely dilated and hypertrophied. When as in this case a large atrial defect opens into the anomalous chamber the hemodynamics are essentially that of a Lutembacher complex with left to right shunt.

Only a few individuals with a fairly large opening through the anomalous septum have reached adult age. The clinical picture is not characteristic. Paroxysmal dyspnea with cyanosis and syncope have been noted in some individuals; others have been relatively asymptomatic until terminal congestive failure made its appearance. Murmurs have been variable or absent. Roentgenograms show right sided cardiac enlargement and pulmonary congestion. The *electrocardiogram* shows right ventricular preponderance. *Catheterization* will reveal pulmonary hypertension and high pulmonary capillary pressure.

It would be possible surgically to remove such an anomalous septum. At the time of operation direct pressure measurements should reveal hypertension in the pulmonary veins but a normal pressure in the main cavity of the left atrium. Direct digital exploration preferably through a pulmonary vein should reveal the anomalous septum which is obstructing the entrance of blood into the left atrial cavity leading to the mitral valve.[34a]

Lesions of the Cyanotic Group

Pulmonary Stenosis with Intact Ventricular Septum and Atrial Septal Defect:[35] The site of stenosis is most frequently valvular but rarely may be infundibular. The septal defect may be of anomalous origin but usually is a foramen ovale which has been forced open by the increased pressure in the right heart. Venous blood is shunted from right to left through the defect The volume of blood in the lungs may be too small to permit adequate oxygenation for the needs of the body especially during exercise. The duration of life depends on the degree of stenosis. Since extreme narrowing to the point of atresia with a closed septum is incompatible with adequate postnatal circulation, intense cyanosis and death early in infancy will occur, life being maintained for a brief time through the presence of a patent foramen ovale and patent ductus. With more moderate degrees of stenosis cyanosis may be delayed until after puberty and may be moderate in degree. Dyspnea may be out of proportion to the degree of cyanosis. Squatting is rare. The course may be stationary for many years although in a minority of the group there may be a rapid progression downhill. Bacterial endocarditis may develop at the site of the stenotic lesion. Death is usually due to congestive failure and anoxia.

A harsh systolic murmur often associated with a coarse thrill is maximum in the pulmonary area. This murmur may be transmitted to the neck and posterior chest. The second pulmonic sound is normal or weak.

The pulse pressure is low. Arterial oxygen saturation is decreased and may fall during exercise if the shunt is of significant size. The circulation time is variable depending on the degree of the shunt and the presence or absence of congestive failure. *Roentgenograms* will reveal a large right atrium and right ventricle. When dilatation of the pulmonary artery is present the pulmonary segment will be enlarged. The vascular shadows in the lungs are frequently decreased (Fig. 12). The *electrocardiogram* may show high P waves, right ventricular preponderance, inversion of T waves in standard Leads II and III and in the precordial leads.



A B

FIGURE 12 Valvular pulmonary stenosis with intact ventricular septum and atrial septal defect *A*, Roentgenogram from seventeen-month-old cyanotic girl in congestive failure, with absent P^2, systolic murmur over entire chest maximum in pulmonary area, right bundle branch block Note marked cardiac enlargement, prominent pulmonary segment, minimal pulmonary vascular shadows. Valvotomy by Dr Julian Johnson was followed by disappearance of cyanosis and of heart failure Systolic pressure in right ventricle at time of operation was 100 mm. Hg; in pulmonary artery too low for measurement After valvotomy systolic pressure in right ventricle was 60 mm and in pulmonary artery 40 mm *B*, Eighteen months after operation. Slight enlargement of heart and pulmonary segment, adequate pulmonary vascularity

Catheterization will show high systolic pressure in the right ventricle which may exceed systemic pressure associated with low pressure in the pulmonary artery. It may be possible to pass the catheter through the atrial defect. *The circulation time from the right ventricle is normal.* Pressure tracings from the right ventricle have a peaked symmetrical appearance (Fig. 2). *Angiocardiograms* will demonstrate hypertrophy and dilatation of the right heart together with stenosis of the pulmonary artery in the region of the valve and dilatation of the artery beyond this point. There may be opacification of the left atrium immediately following that of the right atrium, together with early visualization of the aorta due to the venoarterial shunt (Fig. 13).

Valvotomy or infundibulotomy is indicated in all cases in which cyanosis is present. Following this procedure there is a fall of pressure in the right ventricle associated with a rise of pressure in the pulmonary artery, increased pulmonary blood flow, disappearance of cyanosis and dyspnea and increased exercise tolerance (Fig. 12).

Tetralogy of Fallot (Pulmonary Stenosis; Dextroposition of the Aorta; Interventricular Septal Defect; Right Ventricular Hypertrophy):[36] This is the commonest abnormality in patients with cyanosis who live past puberty. In the minority of cases simple valvular stenosis may exist. In the majority of cases it is the infundibulum that is stenosed, the site of stenosis lying in the mid, low or high position. Valvular and infundibular stenosis may be combined. Finally the developmental error may consist



FIGURE 13 Valvular pulmonary stenosis with intact ventricular septum and atrial septal defect Angiocardiogram from eleven-year-old boy with dyspnea on exertion, slight cyanosis, systolic thrill in suprasterna1 notch and second left interspace, weak P2, systolic murmur maximum in pulmonary area, right ventricular prepor [illegible]
visual [illegible]
artery [illegible]
right [illegible]
marked symptomatic improvement and lessening of cyanosis with no change in cardiac physical findings

of hypoplasia of the entire infundibulum, pulmonary valve and artery. As a result of the pulmonary obstruction and increased pressure within the right ventricle venous blood is shunted through the ventricular septal defect into the aorta which thus receives mixed blood from both ventricles. There is marked diminution in output of blood to the lung because of the pulmonary stenosis and the venoarterial shunt.

Cyanosis sets in relatively early, although it is not necessarily present at birth, and becomes extreme as adult life approaches. Marked clubbing of the fingers, toes, and often of the nose develops. Feeding difficulties are

common in infancy. Development may be slow and growth stunted, although a surprisingly large number of infants with tetralogy may show no impairment of nutrition. Dyspnea on exertion and even at rest is common. These individuals discover early in life that squatting relieves their symptoms of distress. They are subject to attacks of increased cyanosis and respiratory distress sometimes terminating in syncope or convulsions. In infancy these attacks are frequently initiated by feeding. Polycythemia may precede cyanosis or may be slow to develop even in the presence of marked anoxemia and cyanosis. Ultimately it is always present and when sufficiently great is in itself a hazard because of its tendency to produce thrombosis of the cerebral vessels with the development of hemiplegia. Additional complications to be expected are bacterial endocarditis; paradoxical embolus which may result in cerebral abscess if the infected embolus lands in the brain; cardiac failure and functional renal insufficiency.

Cardiac enlargement is slight or moderate. A systolic murmur of variable characteristics may be present along the left border of the sternum, often heard best in the pulmonic area A systolic thrill may accompany the murmur. Both the murmur and the thrill may be absent. The second pulmonic sound may be weak or absent, although in many cases it is of normal or accentuated intensity. As pointed out by Taussig it should never be reduplicated.

Roentgenographic Appearance (Figs. 14, 15): The cardiac shadow is small or only moderately increased in size. In 60 per cent of the cases, especially in infancy, the heart is transversely placed, with pulmonary concavity and a blunt apex which has been likened to the tip of a wooden shoe (coeur en sabot). The hilar shadows are small because of the diminished volume of blood. The peripheral lung fields are free of vascular shadows. If many collateral blood vessels develop in order to supply an additional amount of blood to the lungs, hilar shadows may seem prominent, but if examined closely are seen to be composed of linear aggregates which show no pulsations. The superior mediastinal shadow may be increased to the right by the dilated superior vena cava. In the left anterior oblique position the aortic window will be unusually clear because of the narrowing of the pulmonary artery. The anterior cardiac surface may show increased saliency as a result of the right ventricular hypertrophy. A right aortic arch is present in 20 per cent of the cases of tetralogy of Fallot. In the presence of a normal left aortic arch the trachea and esophagus are deviated to the right at the level of the aortic arch (Fig. 14) whereas they are deviated to the left by a right aortic arch (Fig. 15).

The *electrocardiogram* shows right ventricular preponderance frequently associated with peaked P waves *Catheterization* will reveal high systolic pressure in the right ventricle and low pressure in the pulmonary artery. Since both ventricles and the aorta form an open system the pressure in the right ventricle may equal the pressure in the left ventricle and aorta but cannot exceed it. In the presence of infundibular stenosis it may be possible to demonstrate an infundibular chamber in which only a slight



FIGURE 14. Tetralogy of Fallot with left aortic arch Roentgenograms from seven-year-old cyanotic boy with right ventricular preponderance in ECG Esophagus displaced to right and posteriorly at level of aortic arch Transversely placed heart with concave pulmonary curve and blunt apex, minimal pulmonary vascular shadows, dilated superior vena cava Aortic-left pulmonary artery anastomosis by Dr. Julian Johnson was followed by disappearance of cyanosis and dramatic improvement in exercise tolerance which has persisted for seven years



FIGURE 15 Right aortic arch with right descending aorta At the level of the aortic arch the barium-filled esophagus is displaced to the left in the A-P view but shows no displacement in the right oblique view From a four-year-old girl with tetralogy of Fallot. (Diagnosis proved at operation)

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rise of pressure occurs as compared with the abrupt rise when the main cavity of the ventricle is reached. Pressure curves from the right ventricle are normally asymmetric with a rapid ascent and plateau top (Fig. 2). The oxygen content may be increased high in the right ventricle or pulmonary artery due to a laminated flow of blood from the left ventricle through the ventricular septal defect. It may be possible to pass the catheter from the right ventricle into the aorta. The intracardiac shunt will be directed from right to left, the pulmonary artery flow being less than the systemic blood flow. The pulmonary capillary flow however may exceed the pulmonary artery flow indicating the presence of collateral circulation directed into the lungs.

Simultaneous visualization of the aorta and pulmonary artery in the *angiocardiogram* should not be interpreted to indicate the passage of venous blood from the right ventricle into the aorta if contrast medium is visible in the left atrium and left ventricle owing to a venoarterial shunt through an atrial septal defect.

The first operations designed to increase the blood supply to the lungs consisted in anastomosis of an arterial vessel to a branch of the pulmonary artery. In the Blalock-Taussig procedure a subclavian artery is anastomosed to the corresponding pulmonary artery; in the Potts-Smith procedure the descending aorta is used. Subsequently, Brock introduced the procedure of valvotomy or infundibulotomy through a transventricular approach.

With all of these procedures the immediate improvement following successful operation is dramatic. Cyanosis disappears and exercise tolerance increases; polycythemia decreases and the arterial oxygen saturation rises. Children who were helpless invalids become able to play normally. The possibility of development of bacterial endocarditis, brain abscess, and cardiac failure still exists. The incidence of cerebral complications due to thrombosis and anoxemia should be lessened.

The Brock procedure has fallen into disfavor since the relief of pulmonary stenosis without closure of the ventricular septal defect may flood the lungs with blood under systemic pressure and may lead to the development of pulmonary hypertension. With the development of intracardiac surgery under direct vision aided by extracorporeal circulation it has become possible to attack the stenotic site directly and at the same time close the ventricular septal defect. The operative death rate is high in comparison with the risk of a Blalock or Potts procedure. Moreover, it is often necessary to use a prosthesis to close the ventricular septal defect and to enlarge the outflow tract of the right ventricle. Time alone will give us information concerning the long-term results of the incision in the myocardium and the fate of these prostheses.

Tricuspid atresia associated with a hypoplastic or nonfunctioning right ventricle and with atresia or hypoplasia of the pulmonary artery is a lesion not compatible with any great length of life. Blood entering the right atrium can escape only through an atrial septal defect into the left atrium The size of the right atrium is in inverse proportion to the size of the atrial defect. The left ventricle is the main functioning ventricle. Blood can

reach the pulmonary artery only from the aorta through a patent ductus or from a small right ventricle through a ventricular septal defect Cyanosis appears shortly after birth. The second pulmonic sound is clear with no reduplication. No murmur may be present or a systolic murmur *may be heard to the left of the sternum. If the atrial septal defect is small* and peripheral venous congestion is present the liver may be enlarged. Roentgenograms may show a narrow mediastinal shadow in all positions, a concave pulmonary curve, absence of the cardiac shadow anterior to the aorta if the right atrium is small, and projection of the posterior border beyond the spine in the left anterior oblique view (Fig. 16). If the atrial defect is small the right atrium will be unusually large. Pulmonary vascularity is diminished. The cardiac silhouette, however, cannot always be differentiated from tetralogy of Fallot. A right arch and right descending



FIGURE 16. Tricuspid and pulmonary atresia Very small right atrium and right [illegible] patent ductus arteriosus. From [illegible]

aorta are rarely present. The *electrocardiogram* shows left ventricular preponderance as a rule. In a minority of cases particularly in infants there may be no axis deviation. *Catheterization* reveals increased pressure in the right atrium Although the overall cardiac shunt is from right to left there is sufficient left to right shunt to raise the oxygen content of the right atrium above that of the superior vena cava. *Angiocardiograms* reveal *visualization of the left atrium shortly after the right atrium,* followed by opacification of the large left ventricle In the anteroposterior view a triangular area of non-opacification may be seen at the diaphragmatic surface of the heart in the region usually occupied by the right ventricle

(Fig. 17). There is delayed appearance of contrast medium in the pulmonary circulation.

A Blalock-Taussig or Potts-Smith operation should provide symptomatic relief provided an atrial defect of sufficient size is present. The creation of an atrial septal defect by the Blalock-Hanlon method[37] may be advisable if a small atrial septal defect is present. In such a case high peaked P waves will be noted in the electrocardiogram indicative of the presence of an enlarged right atrium.

Tricuspid atresia may be associated *with transposition of the great vessels* in which case pulmonary stenosis or atresia may or may not be present. When pulmonary obstruction is present, the malformation from the surgical standpoint is physiologically similar to tricuspid atresia without transposition. Benefit can be obtained from a shunt procedure. Cases



FIGURE 17 Tricuspid atresia Angiocardiogram of four-year-old girl with marked cyanosis and dyspnea, soft systolic murmur left of sternum, continuous hum below left clavicle, left ventricular preponderance in ECG. Contrast medium visible in right atrium, left atrium, left ventricle, and large aorta. Triangular shadow near diaphragm in region of right ventricle remains unfilled. Small pulmonary arteries seen after the aorta was visualized presumably filled through a small ductus Creation of an atrial septal defect and right subclavian-pulmonary artery anastomosis by Dr Julian Johnson was followed by marked lessening of cyanosis and increased exercise tolerance

of tricuspid atresia and transposition without pulmonary stenosis, however, have adequate or excessive pulmonary circulation. Physiologically they resemble the Eisenmenger complex in which there is a common ventricular ejectile force for the systemic and pulmonary circulations. The clinical picture in infancy is characterized by pulmonary infections, emphysema and congestive failure. Cyanosis is relatively mild. No surgical procedure is available unless it seems advisable to enlarge the atrial defect.

Eisenmenger Complex (Ventricular Septal Defect; Pulmonary Hypertension; Dextroposition of the Aorta; Pulmonary Artery Normal or Dilated): The ventricular defect is relatively large; the degree of dextroposition of the aorta may vary from a normal degree of overriding to abnormal origin from the right ventricle. The right ventricle is hypertrophied; both ventricles may be dilated.

At birth, because of the large ventricular septal defect the systolic pressure is identical in both ventricles, the aorta and the pulmonary artery. The presence of high pressure in the pulmonary vascular bed results in the persistence of medial hypertrophy in the muscular arterioles in order to maintain high pulmonary resistance. Subsequently intimal thickening develops. As a result flooding of the lungs is minimized and a peripheral flow, adequate to maintain life, can be secured.

The shunt is probably bidirectional from birth, and the aorta and pulmonary artery continuously receive blood from both ventricles. Anoxemia would be present from birth, even though not always of a degree to be visible as cyanosis early in life Since the pulmonary arterial changes are progressive, there is a progressive rise in pulmonary diastolic pressure with ultimate predominant right to left shunt. The oxygen saturation in the pulmonary veins is normal Cyanosis is due to venoarterial admixture and to progressive decrease in pulmonary blood flow as the resistance in the lungs increases.

The infant may present the syndrome of increased pulmonary blood flow (pulmonary emphysema and edema) and die of congestive failure. More commonly a life of average duration with the late appearance of symptoms is possible. The majority die in the third and fourth decade. Cyanosis is late in onset and tends to be moderate in degree with the development of slight clubbing. A loud systolic murmur and thrill may be present to the left of the sternum. If the pulmonary valve is dilated, a diastolic blow may also be heard The second pulmonic sound is accentuated. Squatting is rare. Hemoptyses are not uncommon. Possible complications are bacterial endocarditis and paradoxical embolus. The most frequent cause of death is heart failure. *Roentgenograms* show enlargement of the right ventricle and pulmonary segment, and increased pulmonary vascular markings. The hilar shadows may show expansile pulsations The *electrocardiogram* may be normal or may show right ventricular preponderance. *Catheterization* may reveal identical systolic pressure *in the right ventricle, pulmonary artery, left ventricle, and aorta; and* progressively elevated diastolic pressure in the pulmonary artery. The oxygen content in the right ventricle and/or pulmonary artery may be increased. It may be possible to pass the catheter from the right ventricle into the aorta. *Angiocardiograms* reveal the simultaneous entrance of blood into the aorta and pulmonary artery The left ventricle may be faintly opacified at the same time. The pulmonary artery is usually dilated.

Operation could only be performed under direct vision with the aid of extracorporeal circulation Closure of the ventricular septal defect would

be possible only in early life when the pulmonary arteriolar changes may still be reversible.

Transposition of the Great Vessels:[38] In this condition the relations of the aorta and pulmonary artery to each other are altered at their origin from the ventricles. All degrees of this changed relationship may occur. The ventricular septum normally curves to the right in its upper portion. As a result, if the anterior segment of the membranous septum is absent, the normal aorta will override the ventricular septal defect (*dextroposition;* Spitzer, Type 1). Abnormally the origin of the aorta may be so dextroposed that it arises entirely from the right ventricle which receives blood from the left ventricle through an associated ventricular septal defect. The pulmonary artery arises from its normal position ("simple transposition" of Spitzer, Type 2). Three forms were described by Rokitansky: (1) *complete transposition* ("crossed transposition" of Spitzer, Type 3) in which each great vessel arises from the opposite ventricle; (2) partial transposition in which the aorta and pulmonary artery arise from the same ventricle, but in reversed relationship to each other; (3) *corrected transposition* in which the great trunks rise in reverse relationship to each other, but the ventricle from which the aorta arises receives aerated blood from the pulmonary veins whereas the ventricle from which the pulmonary artery arises receives venous blood The foramen ovale in the right atrium is normally formed, but the right A-V valve usually resembles a normal mitral valve, and the left A-V valve resembles a normal tricuspid valve. Under the term "mixed transposition" (Type 4) Spitzer describes that form of trilocular heart in which a diminutive chamber situated in the right upper portion of the common ventricle gives off the aorta in transposed position. According to Spitzer[38a] transposition is due to a lack of the normal clock-wise torsion of the arterial tube resulting in a reopening of the channel of the reptilian right aorta with obliteration of the left aortic trunk. Saphir and Lev believe that the developmental error is the result of abnormality in the absorption of the bulbus in the stage at which torsion of the arterial trunks takes place. Whatever the embryologic explanation, there is fair agreement that the primary anomaly affects the great vessels and that the association of ventricular septal defect, pulmonary stenosis, etc., is secondary.

Complete Transposition of Great Vessels: The two great vessels arise in transposed position at their origin from the ventricles. Two independent circulations exist, the aorta transporting venous blood from the right ventricle to the body and the pulmonary artery arterial blood from the left ventricle to the lung. Life must be maintained through one or more associated defects which permit oxygenated blood to reach the systemic circulation The age of onset of cyanosis, its intensity as well as the duration of life vary in accordance with the size of the shunt. The pulmonary artery is often dilated, and the pulmonary branches may be prominent. In a minority of cases pulmonary stenosis may be present.

Seventy per cent die in the first year, the majority in the first six months. Cyanosis and polycythemia appear shortly after birth, although they are not always apparent in the neonatal period. Dyspnea, feeding

difficulties, delayed growth, and development are common. The heart size is normal at birth, but cardiac enlargement may become marked within a few weeks. Heart sounds may be loud and clanging. Murmurs may be absent or a systolic blow may be present to the left of the sternum if a septal defect exists

Fanconi[38b] was the first to describe a narrow superior mediastinal shadow in the anteroposterior *roentgenogram* due to the fact that the vessels do not as usual cross over each other but may be superimposed. Taussig pointed out that in the left anterior position the mediastinal shadow in-

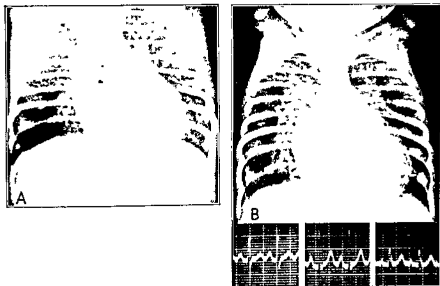


FIGURE 18 Complete transposition of aorta and pulmonary artery in two

creases in width. The superior mediastinal shadow however may be wide when the vessels lie lateral to each other rather than superimposed; in the presence of a large thymus; or when the dilated right atrial appendage projects upward into the superior mediastinum. More characteristic in infancy is the general contour of the cardiac shadow (Fig. 18). The heart enlarges upward so that the superior mediastinal shadow is shortened and displaced upward. There is an oblique downward and outward curve of the left border. Enlargement is due to hypertrophy and dilatation of either the right or left ventricle or both. Intrapulmonary shadows may be prominent if the pulmonary artery is large. In later life the contour may resemble that of tetralogy (Fig. 19) If pulmonary stenosis is associated, transposition of great vessels may be difficult to differentiate from

tetralogy except by angiocardiograms. A right arch and right descending aorta occur rarely.

The *electrocardiogram* usually shows right axis deviation and right ventricular preponderance. Occasionally no axis deviation or left axis deviation may be present.

Results obtained by *cardiac catheterization* are often confusing. The catheter may enter the aorta and cannot be inserted into the pulmonary artery, but this situation may occur in tetralogy. The oxygen content of the aorta is usually similar to that in the right ventricle. It may be

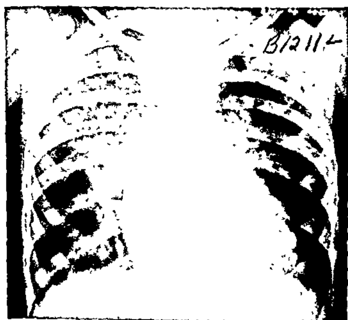


FIGURE 19 Complete transposition of great vessels with large atrial septal defect, dilated pulmonary artery and branches. Roentgenogram of cyanotic eight-year-old girl who died of chronic glomerulonephritis and congestive failure Note vertical heart with contour similar to that noted in tetralogy of Fallot. Excessive vascularity of lung fields

possible to pass the catheter through an atrial defect into the left atrium and compare the pressure in both sides of the heart; or through a ventricular defect into the pulmonary artery. The oxygen content in the pulmonary artery should be higher than in the aorta.

Angiocardiograms (best taken in lateral or left anterior oblique view) show successive opacification of the right atrium, the right ventricle and aorta before the pulmonary artery is visualized. The aorta is seen to rise anteriorly from the right ventricle (Fig. 20). There is poor opacification of the left heart and pulmonary artery.

Surgical treatment is still in the experimental stage. Attempts to transfer the great vessels have failed. Moderate symptomatic improvement may be obtained by the creation of an atrial septal defect by the Blalock-Hanlon method.[39] If pulmonary stenosis exists, anastomosis of a pulmonary artery and arterial vessel may be of value Baffes has obtained

favorable results by anastomosis of the inferior vena cava to the left atrium with the interposition of an aortic graft followed by anastomosis of the right pulmonary veins to the right atrium.[38c]

Complete Transposition of Aorta; Levoposition of Pulmonary Artery (Taussig-Bing Malformation):[39] A large pulmonary artery arises mainly from the right ventricle, but partly overrides a ventricular septal defect. This malformation produces a syndrome clinically similar to the Eisenmenger complex, both great vessels being subjected to pressure at the systemic level.



FIGURE 20. Complete transposition of great vessels with patent ductus A, Cardiac specimen of cyanotic infant who died at two months of anoxia (left

A fair duration of life is possible. Cyanosis is present from birth associated with clubbing and polycythemia. Squatting is rare. A systolic murmur may be present to the left of the sternum. *Roentgenograms* show moderate cardiac enlargement; a large pulmonary segment and prominent pulmonary vascular shadows including many circular shadows of blood vessels standing on end. The *electrocardiogram* shows right axis deviation and right ventricular preponderance. *Catheterization.* It is frequently possible to enter both the aorta and pulmonary artery without difficulty Similar systolic pressure will be found in the right ventricle, aorta and pulmonary artery. There is higher oxygen content in the pulmonary artery than in the right ventricle, aorta or peripheral artery. The *angiocardiogram* (best taken in the lateral view) shows rapid opacification of the right atrium, right ventricle, and aorta together with early opacifica-

tion of the pulmonary artery. The aorta rises anteriorly from the right ventricle.

Symptomatic improvement may be obtained by the creation of an atrial septal defect by the Blalock-Hanlon method.[37] There have been reports of the association of pulmonary stenosis rather than a normal pulmonary artery with this malformation. The clinical differentiation of such a combination from tetralogy of Fallot with marked overriding of the aorta would be difficult if not impossible. Both would probably benefit from creation of an atrial defect plus a subclavian-pulmonary artery anastomosis.

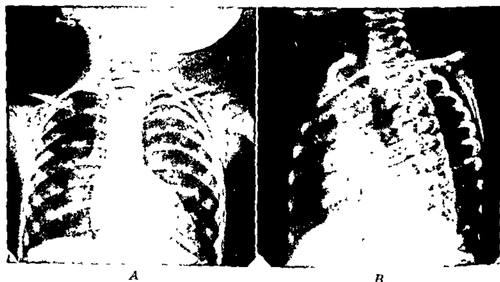


FIGURE 21 Single ventricle with diminutive outlet chamber and transposed great vessels Aorta arising from outlet chamber, pulmonary artery from main ventricle Roentgenogram from three-year-old mildly cyanotic girl with accentuated P^2, mid-systolic click to left of sternum, no murmur, who died at seven years of brain abscess Note convex pulmonary segment in A-P view, no cardiac projection anterior to aorta in left oblique view, prominent vascular shadows

Single Ventricle (Cor Trilocurare Biatriatum):[10] In the great majority of cases the great vessels are transposed. A rudimentary outflow chamber from which either the aorta or pulmonary artery rises occurs in only one-third of the cases. In the remaining cases the common ventricle is divided into subaortic and subpulmonary channels of equal diameter or is not subdivided. The two atrioventricular orifices communicate with the main body of the ventricle.

In approximately half of the reported cases death occurred within the first year. Various individuals with single ventricle and transposed great vessels, however, have lived well into adult life. Abbott has pointed out that in such cases the condition is analogous to that obtaining in the turtle's heart in which streams of blood are directed within the ventricles into their proper channels with relatively little intermingling.

Cyanosis is not always present at birth and tends to be mild when a normal pulmonary artery arises from the main ventricle. In such a case,

however, the lungs are exposed to systemic pressure and pulmonary hypertension must exist. When pulmonary stenosis is present, cyanosis is more severe and the condition clinically is often difficult to differentiate from tetralogy of Fallot. A systolic murmur is usually present to the left of the sternum, occasionally associated with a diastolic blow. The *electrocardiogram* usually shows right axis deviation; occasionally left axis deviation. The *roentgenogram* shows cardiac enlargement often of noncharacteristic contour. Taussig has described a typical contour for a single ventricle with diminutive outflow chamber which shows a conspicuous bulge in the region of the outflow chamber in the anteroposterior view, but no projection anterior to the aorta in the left anterior oblique view (Fig. 21). Pulmonary vascular shadows will be prominent if the pulmonary artery rises from the main ventricular cavity; but diminished if pulmonary stenosis is associated or if the artery arises from a small outlet chamber. The *angiocardiogram shows simultaneous opacification of the* area corresponding to the right and left ventricles with reappearance of contrast medium in the common ventricle after having traversed the pulmonary circulation and the left atrium. Usually a left aortic arch is present. *Catheterization:* It may rarely be possible to pass the catheter from the right atrium through the tricuspid valve into the single ventricle, thence through the mitral valve into the left atrium. The oxygen content of blood from the ventricle and pulmonary artery will be higher than that of blood from the right atrium. The arterial oxygen saturation is decreased.

Persistent Common Truncus Arteriosus:[11] A single large arterial trunk provided with three or four cusps arises from both ventricles above a septal defect and gives off not only coronary and systemic arteries, but also branches to the lungs. If the *pulmonary arteries* arise *from the common trunk* and the lungs are adequately supplied with blood, cyanosis may be slight. The duration of life will vary inversely with the volume of blood shunted into the lungs. If an excessive volume of blood is shunted into the lungs under systemic pressure, death may occur in early infancy due to congestive failure, emphysema and pulmonary edema. If the blood is shunted into the lungs through vessels of moderate size, a fair duration of life is possible. The second pulmonic sound is a single clanging sound. No murmur or a variable soft systolic murmur may be present. *Roentgenograms* will reveal lung fields adequately supplied with blood. This lesion cannot be helped by surgical treatment.

If the right and left pulmonary branches which arise from the sixth branchial arch fail to join the common arterial trunk (*absent pulmonary arteries*) the circulation to the lungs can be maintained only by collateral vessels—usually the bronchial and posterior mediastinal arteries. Clinically this malformation cannot be differentiated from pulmonary atresia with marked overriding of the aorta (pseudotruncus arteriosus). Cyanosis appears early. The degree of incapacity varies inversely with the extent of collateral circulation. If many collateral vessels are present an active life is possible, even though cyanosis may be marked. If few collateral vessels develop, sudden death may occur early in infancy. The second

pulmonic sound is sharp, not reduplicated. Murmurs are often absent but a soft systolic murmur may be audible to the left of the sternum. A continuous hum is often present over some portion of one or both lungs due to the flow of blood through enlarged collateral vessels. *Roentgenograms* show cardiac enlargement with absence of fulness in the pulmonary segment. Taussig has emphasized the abrupt lateral and anterior shelving of the cardiac shadow in infancy (Fig. 22). In later life the contour resembles that of tetralogy. The aortic shadow is large often rising high in the chest. A right aortic arch and right descending aorta may be present. The peripheral lung fields are abnormally clear; fine linear shadows

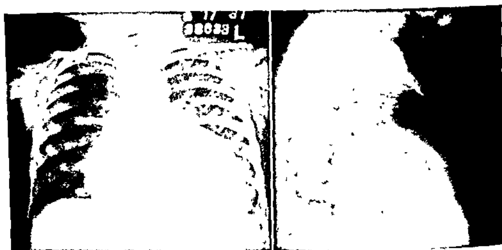


FIGURE 22 Truncus arteriosus Note the horizontal shelving to the left in the A-P view and the anterior shelving in the lateral view From a three-year-old girl with cyanosis who presented a suprasternal thrill, a systolic murmur to the left of the lower sternum, a soft continuous murmur in the right chest, and right axis deviation in the electrocardiogram Died at the age of nine years (terminal illness reported by Solis-Cohen, M, Zaslow, J, and Rabnick, M. H: Am Heart J 28:115, 1944) Necropsy showed an interventricular septal defect 3 cm in diameter; a markedly dilated aorta communicating with both ventricles; no pulmonary artery; a bicuspid right A-V valve with superimposed bacterial vegetations.

of collateral vessels may be seen along the borders of the mediastinal shadow. The *electrocardiogram* shows right axis deviation and right ventricular preponderance. Isolated cases with left axis deviation have been reported.

If a pulmonary artery branch of adequate size is present it may be possible to perform a shunt procedure to obtain symptomatic relief. Especial precautions must be taken at the time of operation to make certain that adequate circulation can be maintained in the opposite lung before an incision is made in the pulmonary artery on the operative side.

When no pulmonary arteries are available for anastomosis, some improvement may be obtained by pleurectomy, followed by the instillation of finely powdered asbestos into the chest with the purpose of producing adhesions which may be penetrated by blood vessels passing from the chest wall into the lung (Fig. 38).

Downward Displacement of Tricuspid Valve (Ebstein's malformation):[12] The leaflets of the tricuspid valve are displaced toward the apex of the heart and usually malformed. The right ventricle is divided into a large thin-walled portion continuous with the right atrium and a small functioning ventricle. In the few reported cases in which cyanosis has been absent the foramen ovale was closed. In the majority of cases the foramen ovale is patent. The primary effect of the anomaly is to reduce the efficiency of the right heart. As the upper chamber cannot empty itself completely, it enlarges progressively. If the foramen ovale is patent,

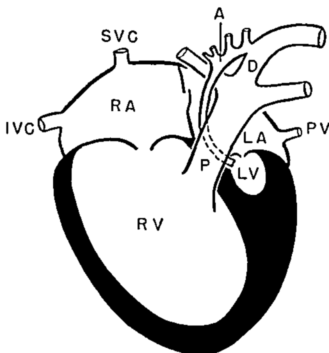


FIGURE 23 Aortic atresia and hypoplasia of left arch *A*, Hypoplastic aortic arch, *D*, patent ductus arteriosus The aorta may arise from the left ventricle as pictured or may terminate blindly within the muscle mass above and to the right of the left ventricular cavity. (From Friedman, S, Murphy, L, and Ash, R: J. Pediat. 38.351, 1948)

venous blood is shunted into the left atrium. The lower chamber which receives less than the normal volume of blood delivers an inadequate amount of blood to the lungs for oxygenation.

Of the first twenty-eight cases reported in the literature twelve had died below the age of seventeen years, three in infancy. Cyanosis was present in all. Of ten individuals who lived past the age of twenty (maximum sixty-one, average forty years) cyanosis was absent in seven. The absence of a patent foramen ovale and of cyanosis would seem to be a good prognostic sign and would influence the roentgenographic findings, since pulmonary vascular shadows would be normal and the heart relatively small.

Cyanosis is occasionally present at birth, but is usually delayed and of insidious onset, out of proportion to the relatively mild dyspnea. Cardiac enlargement is progressive. A variable systolic murmur may be present to the left of the sternum. A mid-diastolic murmur or gallop may be heard over the lower precordium. When cyanosis is present, the *roentgenograms* show a large right heart; concave pulmonary segment; clear lung fields with minimal hilar shadows and a large aorta. The *electrocardiogram* may show right bundle branch block; prolonged PR; arrhythmias; occasional Wolff-Parkinson-White syndrome.



FIGURE 24 Atresia of mitral valve; aortic stenosis, small, undeveloped left ventricle and aorta, small left atrium, patent foramen ovale 4 mm in diameter, markedly dilated and hypertrophied right atrium and right ventricle The roentgenogram shows a greatly enlarged globular heart with fulness in the pulmonic region The lateral view revealed no posterior (left ventricular) enlargement Left axis deviation in the electrocardiogram From a ten-day-old infant with a history of dyspnea and cyanosis of two days' duration Liver enlarged to level of umbilicus Died on the eleventh day

Cardiac catheterization is often difficult and potentially dangerous. Pressure is normal in the right ventricle and the pulmonary artery. It may be possible to pass the catheter through the atrial defect. *Angiocardiograms* show a greatly dilated right atrium which retains contrast medium for a long period; poor visualization of the functioning right ventricle; delayed filling of the pulmonary artery and inadequate opacification of lungs. Contrast medium may be seen to pass through the atrial defect. Occasionally it is possible to visualize displacement of the tricuspid valve to the left.

Since clinically this malformation may resemble pulmonary stenosis with intact ventricular septum and atrial defect, the differential diagnosis is important in order to avoid the error of advising pulmonary valvotomy for individuals with the Ebstein malformation. The electrocardiogram never presents the pattern of right ventricular preponderance characteristic of pulmonary stenosis. In selected cases closure of the foramen ovale for

correction of the right to left shunt may provide symptomatic relief.[42b] Reconstruction under direct vision has been proposed.[42c]

Marked Stenosis or Atresia of the Aortic and/or Mitral Valve with Hypoplasia of the Left Heart:[43] Circulation is maintained by a widely patent ductus through the pulmonary artery which becomes continuous with the descending aorta and thus supplies the systemic circulation with mixed venous and arterial blood, or by a ventricular septal defect. The aortic arch and its vessels may be supplied by retrograde flow (Fig. 23). In addition, some patency of the foramen ovale must be present to permit passage of blood from the left side of the heart. These infants may seem normal at birth, but rapidly develop dyspnea with pallor or grayish cyanosis, greatly enlarged heart and liver, and marked pulmonary engorgement. A systolic murmur may or may not be present. Peripheral pulsations are weak. Death occurs in early infancy. *Roentgenograms* show marked cardiac enlargement with fulness of the pulmonary segment, due to hypertrophy and dilatation of the right atrium, right ventricle, and pulmonary artery, the left ventricle remaining atrophic (Fig. 24). The *electrocardiogram* usually shows right axis deviation and right ventricular preponderance. Isolated cases have been reported which show no axis deviation or left axis deviation.

When mitral atresia is associated with transposition of the great vessels arising from the right ventricle, the prognosis is more favorable.

Vascular Anomalies within the Thorax

Anomalies of Coronary Arteries: (1) *Variation in number and distribution:* Small *accessory arteries* may exist The supernumerary vessel found most commonly arises by a separate ostium behind the right aortic cusp and sends branches to the area of the conus of the right ventricle. It may serve as a source of blood supply from the aorta when other vessels to the heart are occluded. The myocardium may be supplied by a *single coronary artery*. In the commonest type the vessel arises from a single ostium and divides into branches which follow the normal course of the right and left coronary arteries Less commonly a true single coronary artery follows the course of only one coronary artery, usually the left (absent right coronary artery.) Finally, the distribution of a single coronary artery may be entirely atypical. Usually such an atypical vessel is found in association with severe cardiac malformations. The main branches of the left coronary artery may arise from separate ostia instead of from a common trunk There have been isolated reports of *arteriovenous fistulae* connecting a coronary artery and vein and of *aneurysm* of a coronary artery sometimes associated with an arteriovenous communication. Rarely a coronary artery may communicate directly with the right atrium or right ventricle. (2) *Variations in origin:* One or more of the coronary ostia may be situated higher in the aorta than usual. Of more serious significance is anomalous origin from the pulmonary artery. *Origin of both coronary arteries from the pulmonary* artery is rare and results in death shortly after birth Equally rare although compatible with a long life is *origin of the right coronary artery from the pulmonary*

artery. The myocardium receives an adequate supply of blood from the left coronary artery. *Origin of the left coronary artery from the pulmonary artery* however frequently is associated with serious myocardial disturbance.

Origin of the Left Coronary Artery from the Pulmonary Artery:[44] If adequate collateral circulation from the right coronary artery is present individuals with this anomaly may attain adult life. In the majority of cases, however, death occurs in early infancy. At necropsy the heart shows marked enlargement due to hypertrophy and dilatation of the left ventricle. Myocardial degeneration and fibrosis are most marked in the anterior wall of the left ventricle which may develop aneurysmal pouching at the apex. Marked fibroelastic thickening of the endocardium is associated. Pressure of the enlarged heart on the left bronchus results in atelectasis. Infants born with this anomaly are often symptomless for the first weeks of life, after which they may show persistent respiratory distress or transient attacks of sweating, dyspnea, pallor or cyanosis often precipitated by feeding. Death may occur suddenly without preceding symptoms. Murmurs are rarely present.

Inversion of T waves in one or more standard leads of the *electrocardiogram* is a fairly constant finding, but cannot be differentiated from T wave changes which may occur in other conditions associated with anoxia of the left ventricle. The presence of a prominent Q wave in Lead I would favor the diagnosis of anomalous pulmonary artery. The cardiac type of glycogen storage disease which may be associated with inverted T waves in the electrocardiogram may be differentiated clinically by the associated progressive muscular weakness and retardation of development. Glycogen accumulates in striate and smooth muscle as well as in the heart and may be detected by muscle biopsy.

It has been speculated that the absence of symptoms in the early weeks of life in infants with left coronary artery arising from the pulmonary artery is due to some degree of patency of the ductus arteriosus which may have permitted the mixture of arterial and venous blood within the pulmonary artery. Another suggested explanation is that the blood supply of the myocardium becomes inadequate as the activity of the infant increases. This inadequacy would be accentuated by the increasing hypertrophy of the muscle.

Various operative procedures have been proposed. It has been suggested that anastomosis of the pulmonary artery to the aorta will supply more highly oxygenated blood under increased pressure to the myocardium. Such a procedure would almost certainly result in early death from pulmonary edema. Evidence has been presented which seemed to indicate that flow in the anomalous vessel is from the aorta into the pulmonary artery, creating an arteriovenous fistula that fails to supply the myocardium with blood. It has been suggested that ligation of the left coronary artery at its origin from the pulmonary artery would convert the lesion into a single coronary artery supplying both ventricles.[44] Talner et al.,[44b] however, have succeeded in demonstrating the passage of contrast substance from the pulmonary artery into the anomalous coronary vessel by angiocardiog-

raphy. The operation of choice would be transplantation of the anomalous vessel to the aorta with the use of extracorporeal circulation.[44c]

Anomalies of the Aortic Arch:[45] These need not be associated with anomalies of the heart itself although cardiac defects are often present. There may be no symptoms. In such cases treatment is not indicated. Symptoms may be absent in childhood to make their appearance in later life when the vessels become sclerotic. Dysphagia and persistent cough are the most frequent symptoms in adult life, with hoarseness or hemorrhage as rare possibilities. It is possible for a vascular ring to exert pressure on the trachea and esophagus in infancy of a degree sufficient to produce early death. Stridor, the presence of respiratory distress and cyanosis during feeding, dysphagia, and head retraction should lead one to suspect the existence of a vascular ring in an infant.



FIGURE 25 Double aortic arch Roentgenograms in A-P and right oblique views show bilateral esophageal constriction at the level of the third and fourth thoracic

Double Aortic Arch: The right or posterior arch usually is larger; the left, or anterior, smaller. Both arches, however, may be of equal size; or the left may be the larger. The trachea and esophagus are enclosed in a vascular ring formed by the junction of the two arches which unite posteriorly to descend either on the left or right side of the chest. Rarely, one arch is obliterated in whole or in part, represented only by a cord. Bilateral constriction of the trachea and esophagus can be demonstrated by roentgenologic studies made with the aid of barium in the esophagus (Fig. 25). A constricting vascular ring can be severed surgically with relief from symptoms.

Right Aortic Arch: The arch of the aorta passes over the right bronchus instead of the left and lies to the right of the trachea and esophagus. The innominate artery lies to the left and gives off the left common carotid and left subclavian arteries. A rudimentary left arch may persist as a dorsal or ventral diverticulum from which the left subclavian artery and ductus arteriosus may arise.

The presence of a right aortic arch may be diagnosed by roentgenographic means. A pulsating aortic knob or widened superior mediastinal shadow may be visible to the right of the upper sternum. The aortic knob



FIGURE 26 Right aortic arch with retroesophageal and left descending aorta At the level of the aortic arch the barium-filled esophagus is displaced to the left in the A-P view and anteriorly in the right oblique view. From a four-year-old boy with a normal heart

will be absent in the usual left position except in the presence of a diverticulum representing the rudimentary left arch when a small left sided knob may also be visible. The trachea and barium filled esophagus will be displaced to the left in the region of the aortic arch (Fig. 15, 27A).

A right aortic arch may be associated with either a left or a right descending aorta. A left descending aorta passes behind the trachea and esophagus. Roentgenographic examination in the right anterior oblique position, therefore, will reveal anterior deviation of the trachea and esophagus (Fig. 26). The aorta then descends to the left of the spine somewhat more to the right than the normal descending aorta The heart is usually normal in the presence of a right aortic arch and left descending aorta. A right aortic arch with right descending aorta, however, seems to occur predominantly in association with a cardiac anomaly. Approximately 20 per cent of all cases of tetralogy of Fallot are associated with a right aortic arch and right descending aorta. The aorta passes over the right bronchus and descends to the right of the esophagus, usually not crossing over to the left side until it reaches the lower region of the thorax.

It passes through the diaphragm in the normal position Roentgenograms taken in the right anterior oblique position will show no deviation of the trachea and esophagus either anteriorly or posteriorly (Fig. 15)

Anterior deviation of the trachea and esophagus may occur in association with a right descending aorta provided a retroesophageal left aortic diverticulum is present.

When a right aortic arch is present, the fibrosed remnant of the ductus arteriosus on the left may form a ring together with the right arch and pulmonary artery, capable of producing constriction of the trachea and esophagus. This is particularly the case if the ductus arises from an aortic diverticulum. All such constricting rings may be severed surgically.



A *B*

FIGURE 27 Right aortic arch with left subclavian artery arising from right arch and passing retroesophageally Roentgenograms from three-year-old cyanotic girl in whom a right pulmonary artery-aortic anastomosis was performed. *A* (*retouched*), Deviation of trachea to left above carina *B*, Posterior compression of esophagus by retroesophageal vessel

Left Aortic Arch with Right Descending Aorta:[45b] The arch of the aorta takes its normal course over the left bronchus after which the aorta passes retroesophageally and descends to the right of its usual position. In the A-P roentgenogram the barium filled esophagus shows the usual normal indentation on its left margin produced by the arch of the aorta. The esophagus descends far to the left of the midline In oblique views there is anterior deviation of the esophagus in the region of the aortic arch.

Anomalies of the Vessels of the Aortic Arch: The right subclavian artery may arise from the left aortic arch crossing to the right behind the esophagus or in front of the trachea. An anomalous left subclavian artery may pass in a similar manner from a right aortic arch (Fig. 27) or from a dorsal diverticulum associated with a right arch A left common carotid artery may arise from a right ascending arch to pass anterior to the trachea. Either the innominate or the left subclavian artery may leave

the arch at a point further toward the opposite side than usual. The trachea is compressed anteriorly as the anomalous vessel courses upward to reach the apex of the chest. Only in rare instances do such vessels exert sufficient pressure on the trachea or esophagus to produce symptoms. If necessary, they can be divided or displaced surgically to relieve pressure.

Coarctation of the Aorta:[16] The *infantile type* is due to a persistence or exaggeration of the fetal narrowing of that region of the aortic arch which lies between the subclavian artery and the ductus arteriosus (aortic isthmus). If of slight degree the condition is often of no clinical significance.



FIGURE 28 Coarctation of aorta Note deviation of coarcted segment medially; dilatation of ascending aorta and brachiocephalic vessels; poststenotic dilatation of descending aorta From a fourteen-month-old boy with congestive failure.

If extreme in degree or if associated with other serious anomalies death may occur in early infancy. The *adult type* consists of an abrupt, localized narrowing of the descending arch of the aorta at or near the entrance of the ductus. The area of stricture is drawn medially and anteriorly by the ductus (Fig. 28). The degree of stenosis cannot be determined from the external appearance since a diaphragm projecting into the lumen of the aorta may contain only a minute eccentric opening or may be completely closed. Both the infantile and adult type of lesion may be present. The aorta is frequently dilated just beyond the site of stricture. Anomalous origin of the vessels of the aortic arch, bicuspid aortic valves, aortic stenosis, patent ductus arteriosus, or mitral stenosis are not infrequently associated. Aortic insufficiency may develop secondary to dilatation of the aortic arch. Occasional instances of stenosis of the aorta proximal to the

left subclavian artery or more rarely in the lower thoracic or abdominal aorta have been reported.

A more recent classification is based on the relation of the coarctation to the ductus, *i. e*, preductal or postductal and on the patency of the ductus.

With extreme coarctation the entire circulation to the lower part of the body must pass through the subclavian artery by means of anastomoses between the deep arteries of the neck and the aortic intercostal arteries; the internal mammary and the deep epigastric arteries; the spinal branches

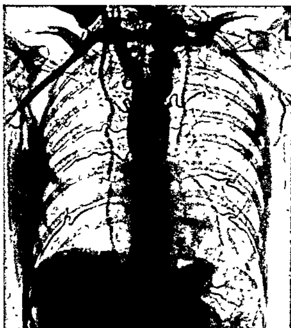


FIGURE 29 [illegible]
the aorta [illegible]
costal arter[illegible]
obvious T[illegible]
phragmatic anastomosis formed by their musculophrenic branches and the phrenic [illegible]

of the vertebral artery and the spinal branches of the aortic intercostal arteries, etc.

The distinctive clinical characteristics which are of vascular rather than of cardiac origin may readily be recognized during life. The individual with coarctation is most commonly a virile male of athletic build Increased pulsations, systolic thrill, and murmurs may reveal the presence of dilated vessels of the collateral circulation in the neck or on the surface of the thorax. These may be especially prominent in the interscapular area. Hypertension of the arms (or more rarely in the right arm only if con-

striction or obstruction of the left subclavian artery is present) will be associated with diminution of the blood pressure in the lower extremities An occasional individual with coarctation may present asymmetry of blood pressure between arms and legs, although the pressure in the arms is within normal limits. Absent or weak pulsations of the abdominal aorta, femoral, and dorsalis pedis arteries will be noted. The heart itself may be normal in size or enlarged to the left. In the absence of aortic insufficiency, especially in childhood, there may be no murmur or only a soft

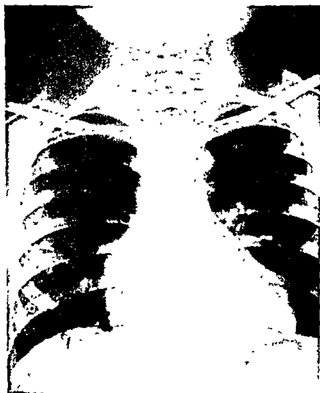


FIGURE 30. Roentgenographic signs in coarctation of the aorta Note indentation of the aorta to the right above the level of the left pulmonary artery with
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A Review

systolic murmur immediately below the left clavicle often heard with maximum intensity posteriorly. Later, systolic murmurs over dilated collateral vessels may be heard over each side of the chest posteriorly and anteriorly, extending down on to the abdominal wall. A mid-diastolic blow may be present to the right of the apex. The second aortic sound may be increased

Roentgenographic Appearance: Scalloping of the inferior surface of the posterior ribs due to erosion produced by the dilated intercostal arteries is a pathognomonic sign but is not always present, even in adult life (Fig. 29). It is absent in the first two ribs, which are supplied from intercostal

arteries arising above the site of coarctation. If the constricted area lies proximal to the left subclavian artery or involves the orifice of this vessel, notching may be noted only in the right hemithorax. The cardiac shadow may be normal or present some degree of left ventricular enlargement. The ascending aorta may be dilated. The dilated left subclavian artery may be visible as a curved outline on the upper left border of the superior mediastinum. It is sometimes mistaken for the aortic knob which is usually absent. It may be possible to note a discrepancy between the increased



FIGURE 31. Coarctation of aorta; saccular aneurysm distal to site of coarctation Angiocardiogram (retouched) and esophagram The arrow points to the site of constriction A=aneurysm, E=esophagus. From a nine-year-old boy in whom the stenosed segment of aorta and the aneurysm were resected by Dr Julian Johnson (Courtesy Dr. Eugene Pendergrass)

pulsations in the left subclavian artery and decreased pulsations in the adjacent descending aortic arch. The descending aortic arch may be traced with difficulty in the left anterior oblique position. Only rarely can the actual narrowing or break in continuity be visualized on the standard roentgenogram When the coarctation lies in the descending arch an indentation or concavity of the aorta to the right may be visible above the level of the left pulmonary artery, with abnormal convexity of the aorta distal to the indentation due to poststenotic dilatation (the 3 sign). There is corresponding deviation of the barium-filled esophagus to the right below the level of the aortic arch with indentation to the left (the ϵ sign) (Fig. 30).[46b] In isolated instances all findings may be negative. In such cases roentgenographic diagnosis is possible only through direct visualization of

the lesion with the aid of contrast substance injected intravenously (Fig. 31) or through the left carotid or brachial artery (Fig. 32).

The *electrocardiogram* may be normal or may show some degree of left ventricular preponderance. Radial and femoral *pulse tracings* will reveal delay in the pulse wave over the femoral artery. *Oscillograms* from the arms show a higher amplitude than those taken over the legs, the reverse of normal. Short or absent K waves may be noted in the *ballistocardiogram.*



FIGURE 32 Coarctation of aorta Arteriogram from eight-month-old infant one-half second after injection of contrast medium into left brachial artery (Courtesy Dr John Hope)

The course in early life is usually symptomless. Characteristic symptoms that may make their appearance in later life are headaches, vertigo, epistaxis, flushing of the face, annoying pain in the chest and shoulders, cramping and intermittent claudication of the legs. The temperature of the skin surface may be higher in the upper than in the lower parts of the body. The most frequent complications are rupture of the aorta; bacterial infection at the site of coarctation or on the basis of associated lesions; cerebral hemorrhage due to rupture of aneurysmal dilatations of the cerebral vessels; and congestive failure, the initial myocardial weakness being frequently induced by intercurrent infection. Only about 25 per cent of the group are destined to live a life of normal duration with death due to unrelated causes.

The coarctation may be resected surgically followed by end to end suturing of the aorta. If the area of stricture is unduly long an aortic graft may

be inserted in adults. Since there is experimental evidence to indicate that an aortic graft will not grow, plastic procedures to enlarge the proximal aortic segment before anastomosis are preferable to the use of a graft in a child. *It is important also that interrupted sutures be used in childhood* since a continuous suture will not permit future growth of the aorta at the site of the anastomosis.

Surgical treatment should be performed in youth: first, because of the relatively early death in at least half the individuals with coarctation; second, because of the increased hazard of hemorrhage in the presence of marked sclerosis and calcification of the aortic arch. Technically the operation is possible in infancy and if intractable failure, marked hypertension or untoward symptoms exist the operation may be performed very early in life. Immediately after operation normal pulsations may be felt in the femoral artery. The fall of pressure in the arms and rise of pressure in the legs may occur more gradually over a period of weeks or months. The apical mid-diastolic blow disappears. Systolic murmurs over the collateral *vessels may persist for a long period of time.*

Coarctation with Congestive Failure in Infancy: Such failure seems re*lated to the absence of adequate collateral circulation at birth. If the site* of coarctation lies distal to the ductus (postductal) the fetus must develop collateral circulation in order to survive and the newborn infant will have no difficulty adjusting to postnatal life. If, however, the coarctation lies proximal to the ductus (preductal) there is no stimulus for the development of collateral circulation in fetal life since the blood takes the usual fetal course from the pulmonary artery through the patent ductus into the descending aorta. Following closure of the ductus after birth sudden strain may be placed on the left ventricle resulting in failure. If the ductus fails to close, the right ventricle persists as the main functioning ventricle and right ventricular failure may result. Many infants with congestive failure *due to coarctation* respond *well to digitalization and might better be* operated on after months or years during which adequate collateral circulation may develop. If they fail to respond to medical treatment recourse to operation should not be delayed unduly.

Anomalous Pulmonary Venous Drainage:[47] Partial anomalous pulmonary venous connection has been discussed with the lesions associated with an arteriovenous shunt.

If *all pulmonary veins empty into the right atrium* the foramen ovale must remain patent. Anoxemia will be present, although cyanosis may be slight or not evident. The systemic circulation is supplied entirely by mixed venoarterial blood through the atrial defect. The left atrium and ventricle are hypoplastic. Arrhythmias (atrial fibrillation or atrial premature contractions) are fairly common. A systolic murmur and thrill *may be present along the left sternal border. Progressive cardiac enlargement* terminates in right sided failure. When all pulmonary veins empty into a *common vessel which empties into the right superior vena cava* by way of the innominate vein, the cardiac silhouette bears a characteristic appearance likened to a figure 8. This common vessel has been termed the left superior vena cava or left vertical vein (Fig. 33). The upper loop

of the figure 8 is formed by the dilated right superior vena cava and left vertical vein; the lower loop by the heart. *Angiocardiograms* will reveal the abnormal course of blood. *Catheterization* shows a significant rise in oxygen content in the blood from the right atrium as compared with the inferior vena cava. The blood from the right superior vena cava may be highly oxygenated. The oxygen saturation of blood from the right atrium will be identical with that in the femoral artery.

This lesion may be corrected by operation under direct vision with the aid of extracorporeal circulation.[17b] An anastomosis is made between the left atrium and the anomalous pulmonary venous channel situated pos-

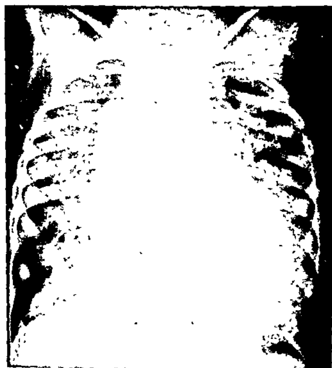


FIGURE 33 Complete anomalous pulmonary venous drainage into the right atrium through a left vertical vein Diagnosis proved by necropsy. Note widening of superior mediastinal shadow due to dilated superior vena cava on right and left vertical vein on left The superior mediastinal shadow and the cardiac shadow form the contour of a figure 8

teriorly. The atrial defect is then closed and the vertical vein ligated. If the left atrium seems unduly small it may be enlarged by displacing the atrial septum into the right atrium.

Anomalous Blood Supply to the Lungs:[18] Anomalous arterial vessels may arise from the thoracic or abdominal descending aorta, from a brachiocephalic artery, usually the innominate or left subclavian, or from the ascending aorta to pass into a pulmonary lobe or into the hilum of the lungs. Vessels which arise from the descending aorta are more likely to be associated with abnormality of the lung (aberrant pulmonary lobe; congenital cyst; bronchiectasis), whereas anomalous vessels arising above

the root of the lung are more likely to be associated with serious cardiac abnormalities, especially absence, atresia or hypoplasia of the main pulmonary artery or absence of one or both pulmonary branches.

Congenital Absence of a Pulmonary Artery Branch:[49] This condition is not too rare in clinics that see many congenital cardiac cases. Associated major or minor cardiac anomalies have been present in practically all cases. There is a tendency for the aortic arch to be on the side opposite the absent pulmonary artery. The lungs are normal. Anomalous blood vessels from the aorta or from a brachiocephalic vessel may penetrate the hilum of the lung which is deprived of its pulmonary artery. Extensive

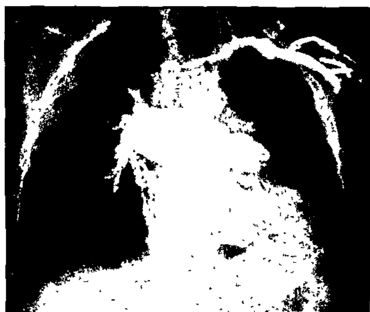


FIGURE 34 Absent left pulmonary artery, coarctation of right pulmonary artery [illegible] contrast medium shows ... onary artery shortly ... visualization of aorta (Courtesy Dr John Hope)

anastomosis of the bronchopulmonary vessels may develop. The hemithorax on the normal side may be smaller than its opposite half Roentgenograms reveal normal vascularization of one lung, whereas the opposite lung is small and relatively avascular. *Angiocardiograms* reveal contrast *medium passing normally through the right heart and main pulmonary* artery into a large normal right or left branch with no visualization of the opposite branch (Fig. 34). Later when the aorta is opacified, a fine network of vessels may appear in the opposite hilar region due to the presence of enlarged bronchial arteries. Occasionally a large anomalous vessel may be seen

Due to the absence of pulmonary arterial circulation normal oxygen exchange does not occur in the involved lung. This may be of significance

surgically if the single pulmonary artery is clamped to perform a shunt procedure. Unless adequate collateral circulation has developed on the opposite side irreversible cardiac arrest may occur.

Bronchial Obstruction Due to Anomalous Course of Left Pulmonary Artery:[53] This syndrome has only recently been described. The left pulmonary artery arises extrapericardially from an elongated pulmonary trunk. It circles anteriorly around the right bronchus and lower part of the trachea, then posteriorly and to the left behind the trachea and in front of the esophagus and aorta. Roentgenograms will show anterior indentation of the esophagus near the level of the carina, constriction of the right bronchus near its origin and deviation of the trachea to the left. Stridor and emphysema of the right chest are associated clinical symptoms.

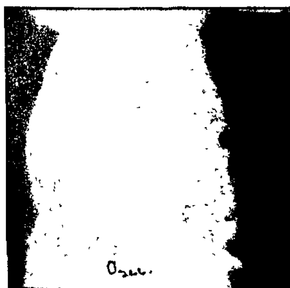


FIGURE 35 Anomalous (absent) inferior vena cava with azygous drainage

Anomalous Inferior Vena Cava with Azygous Drainage (Absent Inferior Vena Cava):[50] This lesion is being found with increasing frequency as an angiocardiographic finding in the diagnostic study of patients with cardiac defects. Contrast medium injected into a saphenous vein enters a vessel which passes upward to empty into the azygous vein (Fig. 35). The hepatic veins enter the right atrium directly. The majority of cases have been associated with partial or complete situs inversus and with serious cardiac lesions. A persistent left superior vena cava has been present in more than half of the recorded cases. The most prevalent lesion in the cyanotic individual has been a biloculate heart with pulmonary stenosis or atresia.

Downing[50b] has described a diagnostic roentgenographic sign consisting of the presence of a rounded density in the right superior mediastinal

shadow which represents the dilated azygous vein as it courses anteriorly to enter the right atrium or superior vena cava.

Pulmonary Arteriovenous Fistula:[51] A congenital pulmonary arteriovenous fistula consists of a network of distended vessels which provide a direct communication between an afferent thin-walled arterial trunk and large efferent veins within the lungs (Fig. 36). Such a fistula may be



FIGURE 36 Pulmonary arteriovenous fistula Angiocardiogram taken one second after *injection of contrast medium shows opacification of right atrium, right ventricle* pulmonary artery, and dilated vascular spaces in lower right lung Faint visualization of aorta due to early return of dye from left lung From a three-year-old cyanotic girl with no murmurs Disappearance of cyanosis followed right lower lobectomy by Dr Julian Johnson. (Courtesy Dr John Hope)

single or multiple and is usually not associated with cardiac disease Polycythemia, clubbing and dyspnea develop as secondary manifestations of anoxemia. Death may result from massive pulmonary hemorrhage. A soft continuous murmur may be heard over the chest wall in the region of the lesion. Roentgenograms will reveal one or more circular shadows within the lung fields which are seen to pulsate on fluoroscopic examination. Eradication may be accomplished surgically.

Dextrocardia

In the broad sense the term dextrocardia[52] is often used to designate all instances in which the heart is found on the right side of the thorax, whether of acquired or congenital origin. The preferable term for displacement of the heart to the right as a result of extrinsic causes is dextroversion. Such displacement may occur in fetal life due to agenesis of the right lung, eventration of the left diaphragm, or congenital cystic disease of the left lung. The heart is normally formed with apex pointed to the left. The term dextrocardia should be reserved for those cases in which

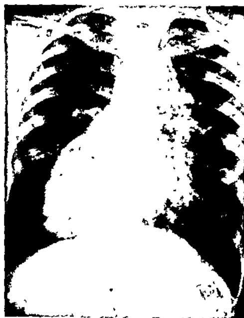


FIGURE 37. Roentgenogram of a child with isolated dextrocardia: The heart lies in the right chest with apex to the right, the aortic knob is situated in the usual position to the left of the sternum The shadow of an anomalous structure (vascular diverticulum?) is visible in the left chest Patient died at fifteen years of meningococcus meningitis No necropsy.

the heart developmentally assumes a position on the right side of the thorax with apex pointing to the right. The perfect example is the mirror image of the normal heart as it is found in complete transposition of the viscera (complete situs inversus). The anteroposterior relations of the cardiac chambers to each other remain unchanged, but the right to left positions are reversed. A right-sided aortic arch and a left superior vena cava are present. In roentgenograms the apex is seen to the right, and the right and left anterior oblique positions replace each other. The electrocardiogram is pathognomonic. All complexes in Lead I are inverted and Leads II and III are interchanged. The frequency of cardiac anomalies in situs inversus is probably similar to that in the population at large.

Isolated dextrocardia due to an arrest of development in an early developmental stage may occur without situs inversus or with incomplete trans-

position of other organs. Grave anomalies of the heart such as pulmonary stenosis, transposition of the great vessels, and single ventricle are frequently present, associated with an incomplete degree of mirror image inversion. The apex is usually directed to the right (Fig. 37). The aortic arch may be found on either the right or left side. The right leaf of the diaphragm is depressed in dextrocardia, indicating that the heart rather than the liver determines the difference in height of the two sides of the diaphragm. The electrocardiogram is often atypical because of the association of cardiac malformation with partial mirror image position. If the



FIGURE 38. [illegible]

[illegible] produced marked improvement in exercise tolerance. Triple operation by Dr Julian Johnson

right ventricle is hypertrophied, a seeming left axis deviation may be present. Inversion of P waves should be present in Lead I but upright P waves may be found if the atrial cavities are not in the mirror image position but retain their usual right to left relationship.

Isolated dextrocardia should not be confused with dextrorotation or incomplete rotation of the heart on its axis (dextrotorsion). In dextrorotation the apex of the heart lies anteriorly within the cardiac shadow usually close to the sternum (Fig. 38). The heart itself may be otherwise normal, but more frequently other anomalies are present, ranging from slight to severe. The electrocardiogram may be modified by the anomaly,

but is otherwise normal except that axis deviation may be modified by changes in the relation of the heart to surrounding structures independent of the effect of ventricular hypertrophy.

Both dextrocardia and dextrorotation of the heart may be associated with anomalies resulting in cyanosis. Among these will be cases of pulmonary stenosis and inadequate pulmonary flow which may benefit from a Blalock-Taussig or Potts-Smith procedure.

Management of the Individual with a Cardiovascular Lesion

The majority of babies with cardiovascular anomalies are asymptomatic and not cyanotic. They should be treated as normal infants and should receive routine immunizing injections although in the delicate infant vaccination against smallpox may be postponed. Because of the great susceptibility to respiratory infection mothers should be cautioned against the danger of exposing these children to individuals suffering from colds. Immediate medical aid should be sought upon the appearance of any infection, however slight.

The cyanotic infant with inadequate pulmonary circulation warrants special consideration. Attacks of paroxysmal dyspnea may be relieved by placing the child in the knee-chest position and providing access to fresh air or oxygen. Severe attacks respond to injections of morphine sulfate in doses of 0.5 to 1.0 mg per ten pounds body weight. An adequate intake of fluid is important to prevent dehydration and lessen the possibility of cerebral thrombosis. If the hemoglobin is low in proportion to the erythrocyte count iron should be administered orally. Cyanotic infants with low hemoglobin who cannot take oral preparations of iron will profit from the intramuscular administration of Imferon. Surgical treatment is not indicated as long as the infant is able to grow and develop even though at a slower than average rate. Young children with tetralogy of Fallot should not be referred for operation merely because of cyanosis and an operable lesion but only if they are definitely incapacitated.

The special liability to the development of bacterial endocarditis and of brain abscess in individuals with cardiovascular anomalies makes it imperative that penicillin be given preceding and following the extraction of teeth, tonsillectomy, etc. All febrile illnesses due to infections should be treated with adequate doses of antibiotics to be continued for one week after symptoms have disappeared. The aim should be to eradicate organisms not merely to treat symptoms. Endocarditis should always be kept in mind as a possible cause for any febrile illness so that the diagnosis may be made early enough to permit adequate trial of the newer therapeutic measures. If it seems probable that a patent ductus is the site of infection ligation or severance of the ductus should be performed after treatment with penicillin or other antibiotics unless the infection is due to a resistant organism or unless heart failure is present in which case operation should be performed early. Cerebral symptoms especially severe headache in a cyanotic individual should arouse suspicion of the existence of a brain abscess due to an infected paradoxical embolus. The combined use of antibiotics and surgical intervention may result in cure.

Since operative procedures of all sorts are well borne, there should be no hesitancy in recommending operations for conditions in which surgery seems indicated.

In early life because of the tendency to malnutrition and susceptibility to infection, careful attention should be paid to the regulation of the daily activity so as to assure proper diet, sufficient rest, and avoidance of fatigue. There is no indication, however, for restriction of exercise beyond the limiting capacity of the heart itself. Patients with congenital cardiac anomalies may be permitted to find their own level of physical activity. In spite of startling murmurs and cardiac enlargement the functional capacity is often normal. An objective attitude on the part of the parents with avoidance of manifestations of sympathy will aid the child to face his difficulties frankly and to recognize both his limitations and his powers. With proper psychologic handling in childhood and definite training toward an income producing occupation, most congenital cardiacs who attain adult life will be able to lead a normal, self-supporting existence. The largest proportion of these will be noncyanotic, but cyanotic individuals also have been known to lead long and useful lives. Cyanotic children, therefore, should by no means be deprived of schooling.

In adult life complications must be treated as they arise. Digitalis should not be used except in the presence of congestive failure. Venesection is sometimes of value in the treatment of hemoptysis, such as may occur in association with pulmonary hypertension. It is to be remembered that in individuals with lesions associated with an arteriovenous shunt tachypnea may be an indication of the increased volume of blood within the pulmonary circulation due to the arteriovenous shunt and not the result of heart failure.

The appearance of an increasing number of procedures directed to the surgical treatment of congenital heart disease has made it imperative that individuals with cardiac anomalies be evaluated to determine whether they need receive the benefit of surgical correction. Cardiac catheterization and angiocardiography are by no means necessary in all cases. In many individuals the diagnosis is obvious without such studies. In others, the anomaly is of little or no clinical significance and elaborate diagnostic tests or surgical procedures are not warranted. The use of such procedures should be reserved for patients with definite cardiac enlargement or symptoms which suggest the advisability of early operation, and in whom the diagnosis cannot be made by routine clinical methods.

Selection of patients for surgical treatment is no simple problem. The clinical status of the patient and the potential hazards of the lesion must be balanced against the risk of operation. There are all degrees of severity of the various cardiovascular anomalies. An individual with a slight degree of pulmonary stenosis or a small ventricular septal defect may be asymptomatic and never require surgical intervention, whereas the presence of a tight pulmonary stenosis or a very large ventricular septal defect may necessitate operation in infancy as a lifesaving procedure. Due consideration should be given to the experience of the available cardiovascular surgical clinic and the facilities for postoperative care. An asymptomatic indi-

vidual capable of living an active life for many years should not be referred for an operation that has not been perfected and carries a high risk.

Finally, psychologic factors should be considered. It is wise not to refer a negativistic child for an elective operation but rather to wait until the child has matured sufficiently to go through the experience without undue psychologic trauma. Time should be taken to discuss the situation fully and honestly with patients or parents so as to make certain that they understand and are willing to accept the risk of operation.

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JOHN R. PAUL, M.D.

6

Epidemiology of Rheumatic Fever

Modern epidemiology concerns the *natural history* of a given disease and the way it seems to behave,—as a mass phenomenon. For purposes of orientation one can approach this aspect of any disease by first attempting to identify and measure the varieties of *circumstances under which it occurs*—whether they be hereditary, environmental (social, geographical), or of many other kinds. So our discussion here of epidemiology will not be limited to considerations of the infectious aspects or to epidemics of rheumatic fever, but rather to its prevalence, its etiology, its ecology, and its geographical, social, and familial pathology.

General Prevalence: The true incidence of rheumatic fever in any given community, the degree of crippling morbidity it inflicts, or the mortality rate justly attributable to this disease is unknown, for its manifestations have not been reflected accurately in mortality statistics, and it is a reportable disease only in a relatively few countries and communities. It is, therefore, not easy to compare its actual prevalence with that of tuberculosis or poliomyelitis. Nevertheless, experience shows that in certain regions it is still among the most important of diseases, although it is becoming less so.

None of the methods which deal with its incidence, prevalence, and general importance is above criticism, but they are the best methods at our disposal From them we find that in the Scandinavian countries, where rheumatic fever is a reportable disease, the incidence per annum has *ranged from about 1 to 3 per 1000 population. From mortality statistics,* we find in this country that there are great variations in time and place which are influenced by such factors as age and race of the patient. Particularly are the differences striking in the white and non-white groups, in which, as Wolff[17] has shown, the non-whites suffer more severely than the whites. From *hospital-admission* figures—which is a rough index of the general importance of a given disease within a given community,—we find that active cases of rheumatic fever make up from 0.1 to 5 per cent of the admissions to the medical services of general hospitals in this country. It is estimated that about twice this figure may apply to children's hospitals. From school surveys, we find that rheumatic heart disease has been detected among school children at a rate of from 0.3 to 6 per cent, and among North American college students from 0 6 to 1 per cent These figures are rough indications as to the general frequency and importance of the disease in this country. On the other hand, the mortality rate

of rheumatic fever is declining both in the United States and England, and so the figures quoted above which were largely gathered in the 1930's can only be said to apply to that period.

Pathogenesis: It has become customary to consider the epidemiology of a given disease from the standpoint of three well known epidemiological similes, the *seed*, the *soil*, and the *climate*. We need not dwell on the first of these three items, for it is today generally agreed that the seed here is the original bacterial incitant, *i. e.*, group A *streptococcus hemolyticus*, and more will be said about this later. As to the soil, (or human susceptibility) it is on this question that the pathogenesis of rheumatic fever and its very nature hinges. Apparently, sensitization phenomena appear to be at the basis of the problem. Thus, it has been a working hypothesis that it is a "conditioning of the human soil" to a special state of *susceptibility* to group A hemolytic streptococci which seems to be responsible in large part for the development of the syndrome known as rheumatic fever.[14]

From the standpoint of the epidemiological *climate*, it is here that recognition is made of conditions peculiarly favorable for the spread of streptococci and for their seeding and growth on "fertile soil" within susceptible hosts, such as "rheumatic" families,[5] or new recruits in the barracks of a naval training station, or other sites where high rates of rheumatic fever have been observed.

The Seed, or Group A Streptococci: Since the primary observations of Coburn,[2] Sheldon,[13] Glover and Griffith,[4] and others in the early 1930's, evidence has continued to accumulate that rheumatic fever is one of the sequellae of the infections caused by Group A *hemolytic streptococci*, which include streptococcal sore throat, acute follicular tonsillitis, scarlet fever, erysipelas, and puerperal fever. Of these, acute streptococcal sore throat and tonsillitis are undoubtedly the commonest forms. This evidence can be drawn from *clinical* and *serological observations*,[12] and from the striking effects which antibiotics exert in reducing the incidence of rheumatic fever when the preceding streptococcal infection receives early treatment.[11] Rheumatic fever follows hemolytic streptococcal infections, particularly of the respiratory tract, as a nonsuppurative complication. Thus, it has been noted that the initial acute illness is usually followed by a latent or quiescent period, which terminates in the more or less explosive appearance of arthritis or carditis (see Figure 1). Recrudescences of rheumatic activity frequently appear when infection by hemolytic streptococci occurs in persons who have previously undergone attacks of rheumatic fever. Immunologic investigations have indicated that high titers of various antistreptococcal antibodies to products and fractions of hemolytic streptococci are usually demonstrable in persons suffering from acute rheumatic fever or from recurrences of this disease.

In many ways then this family of hemolytic streptococci represents *the* seed and can be regarded as *the* etiological agent of rheumatic fever, but to say it is the only etiologic factor is inadequate. The conditioning factor is another aspect of etiology which indicates that children are either born with the capacity for reacting unfavorably, with a special "rheumatic"

response, to streptococcal infections; or that children develop this capacity as an unfavorable response because they are conditioned perhaps, as one theory suggests, by acquiring multiple infections with heterologous types

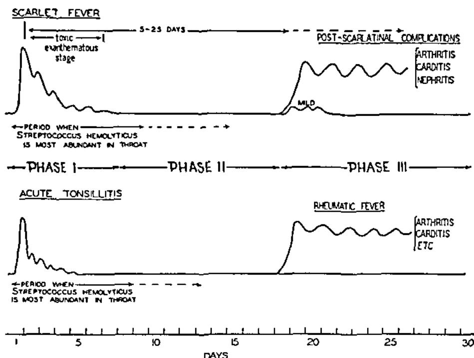


FIGURE 1. Diagram modified from Escherich and Schick to illustrate possible forms which the nonsuppurative "complications" of scarlet fever and of acute tonsillitis may assume. The division of this process into three phases is also shown From Paul [6]

of streptococci early in life. This latter is the direct result of exposure to many *new strains* of streptococci, one after the other, or to *crowding* within the home or bed which facilitates the spread of these organisms and helps to bring about what Coburn has called the "rheumatic state."[2]

These streptococcal infections, which are acquired especially between the ages of one and twenty years, but most frequently in the school age period, are transmitted mainly through human association and through the medium of droplet infection; and to a lesser extent through the medium of contaminated objects, food, or milk. Large numbers of "healthy" carriers exist in the population and are especially numerous among children who play a special part in spreading these infections. Nearly all of these carriers represent actual infections and it is believed that most streptococcal infection is of the latter inapparent type. Immunologic investigation has revealed that in almost eighty per cent of one group of children five to fifteen years of age there was definite evidence of past and recent infection with hemolytic streptococci, as measured serologically by the antistreptolysin (ASLO) test

About three per cent of overt streptococcal infections of the respiratory tract in young adults are complicated by frank rheumatic fever, and consequently wherever a high prevalence of streptococcal infections exists, there is an increased opportunity for a high prevalence of cases of rheumatic fever.

Few more striking demonstrations of the relationship of rheumatic fever to acute hemolytic streptococcal infections can be found than in the programs carried out for the reduction of recurrent rheumatic attacks within cardiac homes for children through the daily prophylactic use of antibiotics; or through the demonstration that a local reduction in the incidence of rheumatic fever can be brought about by the prompt and early treatment of all acute streptococcal infections in a military population as has been done by Rammelkamp and his co-workers at the Francis E. Warren Air Base in Wyoming.[5] These demonstrations prove convincingly that if the "trigger mechanism" can be prevented from occurring or stopped in time by these drugs, then the local incidence of rheumatic fever can be sharply reduced.

The Soil or Host Susceptibility: However, as previously mentioned, it takes factors other than the seed, *i. e.*, other than streptococci, to produce a case of rheumatic fever, and even though group A streptococci may be present in a community and conditions are favorable for their spread, very few cases of rheumatic fever will result unless susceptible hosts are also present in adequate numbers. On this point hinge many questions which concern the nature of rheumatic fever, the crucial one being, What is it that makes one group of individuals (roughly about three per cent) of those infected with *beta hemolytic streptococci* develop rheumatic fever, while another group fails to develop such complications? This leads on to an inquiry as to whether the potential rheumatic patient is so conditioned because of an *inherent* susceptibility, manifest through racial predispositions, anthropological, or familial groups; or an *acquired* susceptibility associated perhaps with conditions which favor repeated infection,[12] or other, largely unknown, factors. It is difficult to assay the relative importance of each.

Racial Susceptibility: As to racial susceptibility or resistance, there is uncertainty because the data on this point are generally unreliable; but Irish people living in and in the vicinity of New York City[6] seem to acquire rheumatic fever somewhat more readily than do representatives of other "races." Negroes do not seem to acquire the disease more readily than Whites in this country but their mortality rate from rheumatic fever is higher.[17]

Anthropological Types: Many investigators believe that certain human types are peculiarly susceptible to the development of rheumatic fever but here, again, data regarding these views are somewhat conflicting.

Familial Incidence: A voluminous literature bears witness to the fact that the prevalence of rheumatic fever and rheumatic heart disease is high in certain families. It has been shown, for instance, that in families in which the parents have suffered from rheumatic fever, the prevalence of this disease is more than twice as high as in other families, and also

that in so-called rheumatic families, eight to ten per cent of exposed persons are infected, as against 2.9 per cent in the families of healthy controls A cogent observation with reference to its familial incidence calls attention to its similarity with that of tuberculosis.

Favoring the importance of *hereditary* factors, Wilson and Schweitzer[15] have corroborated their previous conclusion that susceptibility to rheumatic fever is inherited as a simple recessive trait However, they also point out that the demonstration of hereditary susceptibility does not exclude the operation of environmental factors. It is essentially this same conclusion that was reached in the study of Gray, Quinn, and Quinn.[5] Others have agreed that inheritance played a major role in determining familial aggregation of cases but that a mendelian mechanism could not be established. This is a situation which calls loudly for more study in the field of human genetics, and the domiciliary aspects of rheumatic fever.

A very important point in consideration of susceptibility to rheumatic fever is the factor of age. In its familiar forms *first attacks* of clinically recognizable rheumatic fever occur largely during school age. Susceptibility to both first and recurrent attacks decline in the years after puberty But rheumatic fever cannot be regarded solely as a disease of childhood, for as primary attacks predispose to recurrent attacks, active rheumatic carditis and polyarthritis are common enough during adolescence and young adult life. Nevertheless, from a clinical standpoint the acute forms are uncommon after forty or forty-five years of age. It is also rare in infants under two years, and uncommon under four years. This emphasizes how age conditions susceptibility. The infant apparently must grow up to become "rheumatic", and regardless of close exposure he or she usually succeeds in reaching the age of six or more before the disease is acquired in recognizable clinical forms. This does not mean that the ground work of the "sensitization phenomenon" is not being laid in the years preceding six years of age, which may indeed be one of the most important age periods for conditioning the potential patient for the subsequent acquisition of this disease

A general statement about the age prevalence of rheumatic fever is that the active disease finds its greatest prevalence in childhood, but that, as *primary attacks predispose to recurrent attacks*, the disease continues to be common during adolescence and young adult life. The differing symptomatology exhibited by juvenile and adult patients has also served to give the not altogether true impression that there are two or more distinct forms of the disease, and these features together with the difficulty of differentiating between *first* and *recurrent* attacks have been responsible for divergent views about its age incidence. We refer, for instance, to the child of twelve years of age who comes to the hospital with her first clear-cut manifestation of active rheumatic fever and in whom there is a vague history of growing pains at the age of seven. Which is the first attack? As another example, there is the child of twelve in whom old rheumatic heart disease is discovered for the first time and in whom no history of antecedent rheumatic fever is obtainable.

Slight differences are also apparent in the age of onset, depending upon what the initial clinical manifestations happen to be (Figure 2). Thus, Wilson[16] found in her pediatric group that when the initial manifestation was *polyarthritis* or *carditis* the mode occurred at the age of five. When a *cardiac murmur* or *growing* or *joint* pains were initial manifestations, the mode occurred at age six; with *chorea*, the mode occurred at eight years

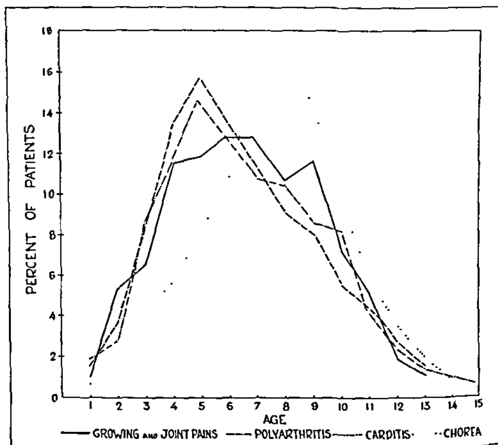


FIGURE 2. Distribution of 674 patients by age at onset and by the type of the initial clinical manifestation From Wilson's series seen in New York City [15]

Sex: Except in the case of chorea, the influence of sex on rheumatic fever is not profound. One finds certain interesting points, however, which have long been recorded in the literature, namely, that in the childhood groups (below age thirteen) rheumatic fever is more likely to develop in girls than in boys, due perhaps to the fact that chorea is commoner in girls. In Wilson's series[16] of 696 patients from a pediatric clinic in New York City, girls represented fifty-six per cent. In adolescent and adult life, active rheumatic fever is said to be more apt to develop in males than in females, but this does not hold for Negroes where females seem to be particularly vulnerable during the child bearing period, not only to severe rheumatic fever with an increased death rate, but also to an actual increase in age specific sex incidence.

The Climate or Environmental Influences: A fundamental question which has long captured the imagination of students of rheumatic fever is its tendency to flourish in high altitudes, in cold damp climates, and in the slums of London or New York. There are apparently few fourth year medical students who are unwilling to discourse on these subjects. But what is known about them? This depends on differential measurements

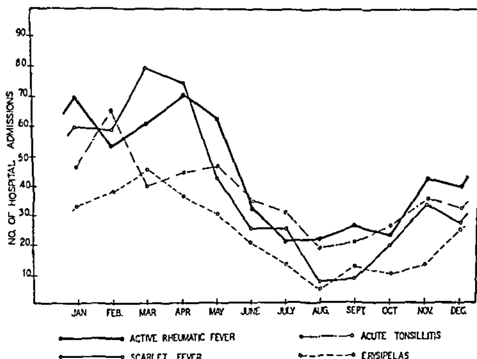


FIGURE 3 Seasonal occurrence of the onset of hospitalized cases of rheumatic fever and of three streptococcal diseases in New Haven County covering the period 1929 to 1938. The rheumatic fever series consists of 526 cases, the scarlet fever series of 458, the acute tonsillitis of 443, and the erysipelas of 285 From Paul[6]

of the incidence of rheumatic fever. Actually, such measurements are not easily made and many divergent opinions have been gained in the past, and continue to be gained, through clinical impressions rather than accurate measurements. As the methods of measuring prevalence all have their failings but some are adequate enough to allow us to indicate that mortality rates of rheumatic fever and rheumatic heart disease differ in different places and have declined in more recent years in England, and in some parts of the United States.[10] Considerable speculation exists as to causative factors which have played a part in this decline. Those suggested include an improvement in living conditions; improved public and personal hygiene; the increased use of antibiotics, and other features. It remains to be seen how real the decline actually is and how long the reduced incidence will be maintained. In any event, we can start with the following premises: Rheumatic fever is common and widespread throughout the world, and, in keeping with the behavior of acute streptococcal diseases,

it flourishes best in cold damp climates as opposed to tropical climates. In the United States there are wide ranges in prevalence reflecting in general a higher incidence in colder and wetter areas in high altitudes.*

The effect of climate is closely linked to seasonal changes and the correlation of streptococcal infections is further borne out here by the fact that the acute stages of illness, i. e., streptococcal infections and rheumatic fever both follow a parallel *seasonal* trend (see Figure 3). This trend seems to differ in different localities, but the greater number of acute attacks of rheumatic fever in the eastern parts of the United States reach a maximum incidence during the late winter and early spring months and, although great variations in incidence occur from year to year, in general a "good" year for streptococcal disease is a "good" year for rheumatic fever.

There have been many attempts to explain the influence of cold and damp weather on this disease or group of diseases, caused not only by streptococci but by other agents responsible for causing respiratory disease. Cold weather in itself would not seem to be a dominant factor, but cold coupled with dampness and also high altitudes, are climatic and geographic conditions which favor the spread of various respiratory infectious disease, particularly under situations which promote crowding within doors. This latter feature, *crowding*, introduces another factor which further complicates the picture but it may be a fundamental one. It may be the explanation why rheumatic fever has been branded, originally in England, as a "social disease," in that it found its highest incidence among the poorer children of industrial towns.[3] This implicated various other factors, exposure to cold and dampness through poor housing, and malnutrition These observations date from the 1920's and 1930's, but have not received the same emphasis today as they did then, perhaps due to the fact that urban living conditions have improved mightily both in England and in the United States during the past two decades. Nevertheless, the effect of socioeconomic conditions on the prevalence of rheumatic heart disease in the United States can still be demonstrated.[9]

The factor of crowding is one to be considered at some length, and it has been since the early and convincing observations of Perry and Roberts in England[7] who established a direct relationship between the degree of crowding and the incidence of rheumatic fever. Rheumatic heart disease furthermore, is still acquired in the United States at a higher rate in school children living in urban than those living in rural areas.[8] In support of the unfavorable effect of crowding are the long-term observations on a group of forty rheumatic and thirty nonrheumatic families by Gray *et al.*[5] It is believed that crowding in the home and bedrooms, allowing, as it does, more intimate contact among younger members of the family group, may be conducive to the spread and maintenance within the family circle of various respiratory infections but particularly those due to hemo-

* The practical significance of the differing rates became manifest during World War II when the experience within Army and Navy installations in various parts of The U S., *i. e*, north and south, sea level and Rocky Mountain areas These revealed different rates for the acquisition of rheumatic fever, and in this respect a correlation with acute streptococcal infection in such areas was established.

lytic streptococci of various types. According to one theory it is this kind of *repeated* infections due to different types of streptococci, within a little cosmos of susceptible hosts, with one infection coming fast upon the heels of another at an age when the child is ill fitted to handle the situation, that this may promote the occurrence of "the rheumatic state." Here is another field which also calls loudly for more investigation

Conclusion: Essentially, the epidemiology of rheumatic fever bears a close relationship to the epidemiology of streptococcal infections, for it is a disease that often follows close upon the heels of a *Streptococcus hemolyticus* infection. It is commoner in cold damp climates and high altitudes. It has found its highest incidence among the poorer classes of urban and industrial populations; it often has a high familial incidence; the period of greatest susceptibility seems to lie between the ages of five and fourteen. However, in view of the fact that the percentage of children or adults who acquire streptococcal infections is large whereas the percentage who acquire rheumatic fever following streptococcal infection is very small, it becomes a major problem of the epidemiologist to continue to seek the explanation of this obscure and basic problem about rheumatic fever.

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CURRIER McEWEN, M.D.

7

Rheumatic Heart Disease

Etiology: Rheumatic heart disease is part of rheumatic fever, the etiology of which is not yet fully known.

Many different microorganisms have been considered responsible for the disease, including filterable viruses and even the tubercle bacillus. At present, however, all evidence points to hemolytic streptococci of group A as the responsible agents,[1,2,3] although it is not clear why some individuals infected with these microorganisms develop rheumatic fever while others do not.

The mechanism by which hemolytic streptococcal infections lead to rheumatic fever is also unknown. There are currently several theories which may be mentioned According to one, the underlying mechanism is that of delayed hypersensitivity to streptococci or their products. According to a second, the disease results from auto-antibodies to the patient's own tissue proteins which have been altered by streptococcal action. A third theory invokes the action, either direct or through the mechanism of delayed hypersensitivity, of a hypothetical specific toxin or enzyme common to "rheumatogenic" hemolytic streptococci. According to a fourth theory, the disease is due to direct invasion of tissues by hemolytic streptococci. Finally, a modification of the last theory assumes that valvular damage results from direct action of hemolytic streptococci lodged in the cardiac tissues but that the manifestations of the acute stage of disease are dependent on a separate mechanism such as one of those noted in the first three theories cited above.

There are certain *predisposing causes.* Rheumatic fever is known to occur more frequently in temperate climates. Like measles and scarlet fever, it occurs in cycles, but this is related to the cyclic incidence of group A hemolytic streptococcal infections. There is a seasonal variation, the greatest incidence in America being in the late winter and spring, while in England the incidence is somewhat greater in autumn It has been frequently pointed out that the family incidence of the disease is high. To what extent this is due to cross infection, to inherited susceptibility, or to environmental factors is not definitely known, but it is probable that all three play a part. While the disease is seen moderately frequently among well-to-do patients living in good hygienic surroundings, it occurs much more frequently among the poor who live in want and under crowded conditions. The age of the patient is also a factor. In childhood and in early adolescence, the heart is more apt to be affected than later in life. Adults

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with first attacks of rheumatic fever also sustain cardiac damage but less frequently and less seriously than children.[4]

Structural Changes: Rheumatic heart lesions are spoken of as being active or inactive, depending on whether inflammation is present or merely scar tissue resulting from previous inflammation. They may be in the pericardium, endocardium, or myocardium.

Pericarditis: The pericardium loses its glistening appearance, becomes congested, coated with fibrin, and roughened. Endothelial cells swell; new blood vessels are formed. Probably in all cases there is some serous exudate. If the amount is great enough to cause physical signs or x-ray changes, the patient is said to have pericarditis with effusion.

During either the fibrinous or the effusive state, resolution may take place. This may result simply in a cicatricial thickening of the pericardium without adhesion; or, in the process of healing, adhesions may occur between the visceral and parietal layers of the pericardium, or between the parietal layer of the pericardium and the pleura, mediastinal structures, or diaphragm.

Endocarditis: The term endocarditis is generally used in a loose sense to mean inflammation not only of the endocardial lining of the valve, but of the entire valve structure—a meaning which is much more accurately expressed by the term valvulitis. True endocarditis does occur, however, as part of valvulitis and as localized inflammation of the mural endocardium, especially of the left auricle. The earliest change in rheumatic valvulitis appears to be localized edema in the depth of the valve, with cellular infiltration and proliferation following rapidly. On the surface, usually at the line of apposition of the valves, small areas of necrosis appear, on top of which thrombi are laid down, composed of fibrin and platelets. These can be seen grossly as small pinkish-yellow vegetations on the valves and chordae tendineae. As the process increases, cellular proliferation and new capillary formation occurs, particularly at the base of the valve, so that much of the valve becomes the seat of a chronic granulomatous inflammation. Healing takes place by organization and scar formation, with the result that the valves become thickened, shortened, and distorted. These changes prevent the proper closure of the valve and cause regurgitation. The same deformities plus fusion of the valve margins, and sometimes calcarious deposition, interfere with the normal passage of blood through the orifice and cause stenosis.

Myocarditis: Probably the earliest lesion is a biochemical or physical chemical change in the mesenchymal ground substance between connective tissue fibrils, particularly in the walls of the smaller blood vessels. Other early changes consist of focal areas of edema and cellular infiltration. This exudative stage is followed by that of proliferation characterized by the formation of Aschoff bodies. These focal collections of cells are found most frequently in the basal portion of the ventricular wall, are usually perivascular, and located in the subendocardium, but may be anywhere in the atrial or ventricular myocardium. The Aschoff bodies are characterized by large, basophilic, often multinucleated cells, the nature of which has received much study.[5,6] After the active inflammation has subsided, the nodules

gradually become small foci of fibrous tissue, but study of atrial biopsy specimens obtained at operations has shown that Aschoff bodies may persist years after all clinical evidence of disease activity has subsided.[6] Although these characteristic lesions are focal in distribution, the myocardium is diffusely weakened and dilatation occurs. Contrary to what is often thought, the course of rheumatic heart disease clearly indicates that the myocardial damage and not that in the valves is chiefly responsible for the appearance of heart failure in the active stages of this disease, especially in early attacks.

Symptomatology: From this brief description of the morphological changes it will be seen that there are two stages of rheumatic heart disease, the active and inactive. Active rheumatic heart disease, or carditis, is the stage of active inflammation. Inactive rheumatic heart disease is the stage of purely mechanical damage resulting from the scarring left as a consequence of the earlier inflammation. Any discussion of symptomatology of rheumatic heart disease must consider these two stages separately, and since the inactive stage can be covered more briefly it will be considered first.

Inactive Rheumatic Heart Disease: Although there are very distinct physical signs of inactive rheumatic heart disease, strictly speaking, there are no symptoms, for when symptoms occur they are those resulting either from a cardiac arrhythmia or from heart failure. Many patients with inactive rheumatic heart disease have no symptoms at all, while others experience various degrees of cardiac insufficiency ranging from mild dyspnea on exertion to severe congestive heart failure even at rest. In view of the permanent valvular deformities, pericardial adhesions and myocardial scarring, it is to be expected that symptoms of heart failure would occur; and one of the most striking features of inactive rheumatic heart disease is the paucity of such symptoms so long as the functional capacity of the myocardium remains good. Symptoms and signs of heart failure promptly appear, however, when the myocardium is weakened by a new attack of carditis or by the degenerative changes of advancing years. Among the arrhythmias which may appear in inactive rheumatic heart disease, auricular and ventricular premature contractions are the most common. Next in frequency is auricular fibrillation but, in this connection, it should be pointed out that the appearance of this arrhythmia in a rheumatic patient under forty years of age is presumptive evidence of a return of the active inflammation.

Although the common type of pain which occurs in rheumatic heart disease is that of carditis, there is a less common type which can occur also in inactive rheumatic heart disease. This pain is anginal in type, often excruciating and often radiates to the left shoulder and arm. It frequently is associated with sudden elevation of blood pressure and is relieved by amyl nitrite. It occurs in patients with aortic insufficiency and aortic stenosis and probably is caused by myocardial anoxemia resulting from inadequate coronary filling.

The physical signs of inactive rheumatic heart disease are those of the various valvular defects and of cardiac enlargement (*q.v.*).

Active Rheumatic Heart Disease (Carditis): As this is merely one manifestation of rheumatic fever, other evidences of that disease usually make their appearance, such as fever, polyarthritis, subcutaneous nodules, chorea, pleuritis, and erythema marginatum. When these are obvious, the nature of the disease is easily recognized. Even without the presence of other manifestations the diagnosis of rheumatic carditis usually is readily made if it is severe, for attention is drawn to the heart by such symptoms as dyspnea and precordial pain. In some patients, on the other hand, carditis may be insidious and other rheumatic manifestations either lacking or consisting merely of such vague complaints as aching joints, fatigability or loss of appetite. The diagnosis in such cases is easily missed and the patient must be watched with great care for the appearance of definitive signs or symptoms. This is particularly true in children in whom rheumatic carditis is prone to develop insidiously.

In discussing active rheumatic heart disease, the term *carditis* is especially appropriate because it connotes the important fact that all parts of the heart—myocardium, valves, endocardium, and pericardium—are involved. Nevertheless, involvement of the various parts of the heart tends to be associated with particular symptoms and signs and in describing the symptoms of carditis it is useful to take up those caused by lesions of the myocardium, valves, and pericardium separately, although it must always be borne in mind that all occur together in most cases.

Myocarditis: Because the murmurs which accompany rheumatic valvular damage are so striking and because they persist into the inactive stage of rheumatic heart disease, early writers tended to stress the valvular lesions and to underestimate the importance of the myocardial damage. It is now well appreciated, however, that the myocardial involvement is much the more important so far as the functional capacity of the heart is concerned during the course of carditis. This is apparent when one considers the many patients with severe congestive heart failure during the course of carditis who later have excellent cardiac reserve when the carditis has subsided, in spite of the persistence of the valvular defects. Thus, *heart failure* developing during the course of rheumatic fever is, in itself, an important indication of myocardial involvement. Other signs and symptoms of myocarditis are the rapid development of *cardiac enlargement, precordial pain* and *tenderness*, the development of an apical protodiastolic *gallop, tachycardia* out of proportion to the degree of fever, and various *electrocardiographic changes*. Furthermore, since rheumatic pericarditis and valvulitis rarely, if ever, occur without myocarditis, any evidence of cardiac involvement during rheumatic fever suggests the presence of myocarditis.

Valvulitis: Although the term "endocarditis" is used to designate involvement of the mural endocardium which is so common in rheumatic carditis, it has been largely replaced by the term "valvulitis" in speaking of rheumatic inflammation of the cardiac valves. As was pointed out in the discussion of structural changes this designation is a more accurate one, for the entire valve substance is involved. Mitral insufficiency is the commonest valvular lesion, clinically. Second in frequency is mitral stenosis

which is the most characteristic valvular lesion of rheumatic heart disease Aortic insufficiency and stenosis are also common, and damage to the tricuspid and pulmonic valves is demonstrable pathologically but is difficult to diagnose during life. These various valvular lesions usually are permanent once they appear, but they may be transient if the valvulitis subsides before too great proliferative changes have taken place. Murmurs early in the course of carditis probably are due to relative dilatation of a chamber or of a valve ring and to edema of the valve leaflets. Probably true stenotic deformities do not occur until after weeks or months of valvulitis. Other signs associated with mitral valvulitis are an accentuation of the second pulmonic sound, and the so-called opening snap, but these also appear only after the valve has been diseased for some time.

Systolic Murmurs appearing during the course of rheumatic fever should lead one to suspect the presence of valvulitis but do not provide definite evidence unless distinctly "organic" in character because they are so common in other infectional diseases unassociated with cardiac damage. The appearance of *new diastolic murmurs*, on the other hand, is conclusive evidence of valvulitis

Pericarditis: While pathological studies show that some degree of pericarditis occurs in most cases of active rheumatic heart disease, clinically important or diagnosable pericarditis is less common than myocarditis and valvulitis. It is more frequent in children than adults Because of the danger of cardiac tamponade, patients with pericarditis must be watched with particular care.

The most conclusive evidence of pericarditis is the appearance of the typical *pericardial friction rub.* This is usually heard first in the region of the apex and along the left sternal border but is sometimes loudest at the base of the heart. In its most characteristic form it is a to-and-fro grating sound not quite synchronous with the heart sounds. It may be heard for only an hour or two or may persist for days. Conclusive evidence of pericarditis is provided also by certain *electrocardiographic changes* described under Electrocardiography.

Of merely presumptive significance are precordial pain and signs suggesting effusion. *Pain* may vary from precordial soreness to a sharp, stabbing, pleurisy-like pain.

Pericardial effusion is suggested by the following: (*a*) Radiographic demonstration of an enlarged pyriform cardiac shadow extending up to the first and second ribs to both the left and right of the sternum, with obliteration of the cardiovascular angle; (*b*) increase in areas of cardiac dulness, particularly at the base of the heart in the first and second interspaces; (*c*) diminution in intensity of the heart sounds; (*d*) displacement of apex beat upward and to the left; (*e*) signs of consolidation (*Ewart's sign*) at the base of the left chest posteriorly. The latter are caused by pressure of the enlarged pericardial sac on the left lung. Aspiration of pericardial fluid of course makes the diagnosis definite.

Signs and Symptoms of Carditis· Probably the most important single factor in the management of a patient with rheumatic heart disease is the determination whether the disease is in the active or inactive stage. Be-

cause of this importance, the various signs and symptoms of carditis are summarized below. Among the *conclusive evidences* are: (*a*) The appearance of heart failure during the course of rheumatic fever; (*b*) the development of new diastolic murmurs; (*c*) the appearance of a pericardial friction rub; and (*d*) significant increase in the size of the heart—all if they occur during an attack of rheumatic fever. Among the *presumptive evidences* are: (*a*) Tachycardia out of proportion to fever; (*b*) gallop; (*c*) precordial pain and tenderness; (*d*) the presence of subcutaneous nodules; (*e*) significant increase in the atrioventricular conduction time; (*f*) the development of auricular fibrillation or congestive failure in any patient with physical signs of rheumatic valvular defects, especially in patients under forty; (*g*) fever, leukocytosis, or increased erythrocyte sedimentation rate in any rheumatic patient in whom there is not some other clear explanation for their presence, and (*h*) the appearance of any manifestation of rheumatic fever in any patient, for the heart must always be assumed to be involved until it has been shown not to be. Of course some of these presumptive signs and symptoms should make one merely suspect the presence of carditis whereas others, and especially combinations of them, are practically conclusive.

Electrocardiographic Findings: These have been referred to in discussing myocarditis and pericarditis. They are considered more fully in a later section.

Course of the Disease: The stage of active carditis varies in length from a few weeks to several years and in severity from episodes which escape the notice of even a careful physician to attacks which are fulminating and cause death in a few days. In the great majority of patients, however, the disease gradually passes into the stage of inactivity: symptoms of inflammation disappear; temperature, leukocyte count, and erythrocyte sedimentation rate become normal; anemia improves, and symptoms of heart failure clear.

During the inactive stage of the disease, a diminished cardiac reserve may or may not be present. Many patients for years show no such diminution; and when frank failure occurs it usually means that active carditis has reappeared or that the patient has reached the age group in which degenerative changes in the heart contribute to cardiac insufficiency.

It will be seen that rheumatic heart disease may be associated with cardiac insufficiency in either its active or inactive stages. During the period of activity, such diminution may be due to inflammation of the myocardium, causing inefficiency of the muscle, or to the changes brought about by the increased pressure in the pericardium in pericarditis with effusion. It is probable that the endocardial lesions play a comparatively small part in the loss of cardiac efficiency during the early active phase of rheumatic inflammation.

During the inactive stage of the disease, the changes which contribute to diminished cardiac reserve and congestive heart failure are pericardial adhesions binding the heart to the adjacent structures, fibrotic changes in the myocardium, and, most important, scarring of the chordae tendineae and the various valves, resulting in valvular incompetence or stenosis and

thus affecting the dynamics of circulation. During either of these stages, changes in the various functions of the heart muscle may result in one or another of the arrhythmias and they, in turn, may become a factor in further producing heart failure.

From the foregoing, it is clear that active rheumatic heart disease (carditis) is vastly more important than the inactive form, for the latter occurs only as the result of the former and is made progressively worse by repeated attacks. Thus, the course and prognosis in any given case depend mainly upon three factors: The severity of the attacks of carditis, how long they last, and how often they are repeated. On the basis of these factors four clinical types of course may be described.

Acute Fulminating: In this type, the disease runs a rapid course with high temperature, high leukocytosis, marked signs of heart failure, and death within a few days to a few months. Fortunately, it is rare, especially in adults In an analysis of seventy children admitted to Bellevue Hospital in their first attacks of rheumatic fever prior to 1943, three cases (or 4.3 per cent) ran this type of course whereas there were no such cases among sixty-seven adults[4] More recent experience has been even more favorable.

Chronic Active: In this type the patient develops active rheumatic carditis the evidences of which diminish but never entirely disappear. Such patients usually have diminished cardiac reserve, more or less anemia, fatigue, and low-grade fever, but active inflammation may be so low grade that it is not recognized. Carditis of this type may continue for years and end in death without ever subsiding, or the disease may eventually become inactive.

Recurring: This is the most frequent clinical type. Periods of activity occur every few years, separated by longer or shorter periods of inactivity. During the periods of inactivity, particularly early in the course of the disease, there is usually no diminution in the cardiac reserve.

Persistently Inactive: In this clinical type, carditis heals with or without residual damage after a few weeks or months and does not return In the past, such fortunate outcomes were not common and occurred in adults more often than in children. Today, however, it is the aim of continuous prophylaxis to make all attacks of this type.

Diagnosis: In typical cases of active rheumatic heart disease, especially when polyarthritis or other rheumatic manifestations are present, the diagnosis is obvious from the start. Often, however, the diagnosis is obscure and a correct conclusion can be reached only after careful observation of the patient over a period of days or weeks.

In general there are four types of diagnostic questions which arise. First, in a case of definite rheumatic fever, one must decide whether or not the heart is involved This is done by looking carefully for the various presumptive and conclusive evidences of carditis, meanwhile keeping the patient in bed.

A second type of problem is that of the child with vague symptoms that might be rheumatic but are not clearly defined. Again one must watch for the development of distinct signs or symptoms.

A somewhat similar problem is posed by the patient known to have inactive rheumatic heart disease who begins to have vague symptoms. It may be difficult to determine whether a new attack of carditis has occurred or whether the patient merely has some incidental illness. Once more, the only solution is to keep the patient at rest while searching carefully for the various signs and symptoms of rheumatic fever and carditis.

A final and common question is that presented by the patient with old valvular disease of which one must decide the underlying etiology. Usually this is not difficult because the combination of a past history of rheumatic fever and the physical signs of mitral stenosis point to a rheumatic basis. Even in the absence of a rheumatic history, the presence of a characteristic apical diastolic murmur usually is diagnostic although there are some exceptions as noted under Differential Diagnosis.

Differential Diagnosis: The question of differential diagnosis usually is not a difficult one However, carditis can be simulated by a number of diseases including bacterial endocarditis, sickle cell anemia, leukemia, brucellosis, and hyperthyroidism. Other types of pericarditis can also cause difficulty as can congenital heart disease.

Bacterial Endocarditis is apt to be especially confusing because it is so often implanted on valves previously damaged by rheumatic fever. Usually, however, the appearance of embolic phenomena and positive blood cultures make the correct diagnosis clear.

Sickle Cell Anemia and Leukemia may lead to confusion because of the aching which may occur in muscles and joints, and the anemia, murmurs, and cardiac enlargement which often accompany it. The true nature of disease is, of course, readily shown by suitable examination of the blood.

Brucellosis and other low-grade chronic infections may simulate rheumatic fever with carditis and only prolonged observation may reveal the correct diagnosis.

Hyperthyroidism without obvious thyroid enlargement or exophthalmos sometimes is mistaken for rheumatic carditis because of its accompanying tachycardia, forceful heart action, and low-grade fever. Occasionally there may even be a slurring of the heart sounds at the apex which can be mistaken for a rumbling diastolic murmur. This sound and the other symptoms disappear, however, under suitable antithyroid therapy.

Pericarditis due to tuberculous infection can usually be differentiated by other evidence of tuberculosis. Non-specific pericarditis usually is diagnosed only by excluding the tuberculous, pyogenic, and rheumatic types, unless a specific virus is isolated from the pericardial exudate.

Postscarletinal Carditis used to be considered a distinct entity, but today it is accepted that it is true rheumatic carditis following a hemolytic streptococcal infection in the form of scarlet fever.[8]

In *inactive rheumatic heart disease*, the commonest differential problem is that presented by the patient with a negative rheumatic history and with aortic insufficiency and a rumbling diastolic murmur at the apex. It is sometimes impossible to determine whether such a patient has inactive rheumatic heart disease with aortic insufficiency and mitral stenosis or syphilitic heart disease with aortic insufficiency and an Austin Flint mur-

mur at the apex. In such cases it is helpful to compare the intensity of the aortic diastolic murmur at the second right interspace and along the left sternal border with the patient upright and recumbent. In syphilitic aortic insufficiency the murmur tends to be louder at the second right interspace with the patient upright than at the left sternal border with the patient flat, whereas in rheumatic aortic insufficiency the reverse is true.[9] Occasionally, also, congenital lesions are difficult to differentiate from rheumatic ones, and in a patient with a vague incidental infection, may even lead to a suspicion of rheumatic carditis.

Complications: *The principal complications of rheumatic heart disease* are (*a*) abnormalities of rhythm of which auricular fibrillation is most important; (*b*) embolism; (*c*) bacterial endocarditis; and (*d*) heart failure

Especially in patients under forty years of age, the onset of *auricular fibrillation* is apt to mean that a new attack of carditis has begun, but it occurs frequently also in inactive rheumatic heart disease. Early in the course of rheumatic heart disease auricular fibrillation may be transient but when it occurs in hearts already seriously damaged it usually is permanent.

Embolism, usually from mural thrombi in the left atrium, can occur at any stage of the disease but especially in long established cases. It can result in merely mild symptoms or in such serious accidents as cerebral embolism or saddle embolism with thrombosis of the iliac arteries. Among 3129 patients with rheumatic heart disease followed up to the time of death, death was attributed to embolism in 2.8 per cent.[10] Cerebral accidents caused death in another 2.9 per cent and some of these undoubtedly were due to cerebral embolism. These figures are very incomplete, however, for they do not include instances of nonfatal embolism.

Bacterial endocarditis may be implanted on rheumatic valves as it may on valves abnormal from other causes. It occurred in approximately 9 per cent of 3129 patients with rheumatic heart disease.[10]

Heart failure of the congestive type is so much a part of the disease picture that it is scarcely thought of as a complication. Heart failure of the anginal type occurs also though less commonly and paroxysmal nocturnal dyspnea is occasionally a major therapeutic problem. These are discussed elsewhere.

Treatment: ***Treatment of Carditis:*** *It is essential in the treatment of* active rheumatic heart disease to appreciate that one is dealing with an inflammatory process and with one which results from an infection. Various symptoms require treatment, but much more important are measures directed toward helping the patient overcome the infection and toward combating the inflammation. Happily, the *antibiotics* provide us today with powerful means of overcoming the inciting hemolytic streptococcal infection, but the problem of overcoming the rheumatic inflammatory process in the heart remains one which has not been solved. To be sure, the powerful antirheumatic action of *salicylates* and of *corticosteroids* and *corticotropin* on the inflammation in the joints and on the fever and general "toxicity" of rheumatic fever is thoroughly established. Unfortunately, however, the effect of these drugs and hormones on

rheumatic inflammatory process in the heart is much less convincingly beneficial. The use of these agents and of other measures in the treatment of rheumatic heart disease is discussed in the paragraphs which follow.

Eradication of the Hemolytic Streptococcal Carrier State: In any patient with active carditis—or any other manifestation of rheumatic fever—an initial aim is to eliminate any viable hemolytic streptococci which the patient may carry. It has not yet been proved whether antibiotics can benefit rheumatic fever directly, but it is certain that they can eliminate the hemolytic streptococci which incite the disease and keep it active. For this purpose *penicillin* is the drug of choice. It may be given in several ways: (1) Intramuscularly in the form of *benzathine penicillin G* as a single injection of 1,200,000 units; (2) intramuscularly in the form of *procaine penicillin in oil* with 2 per cent *aluminum monostearate* in doses of 600,000 units every third day for three doses; (3) orally in doses of 500,000 units daily in two divided doses for a period of ten days. Any one of these methods is adequate to eliminate the carrier state in the great majority of cases.

Recently, Rammelkamp and his collaborators[11] have hypothesized that the late valvular damage of rheumatic fever results from the persistence of viable hemolytic streptococci in the cardiac tissues for prolonged periods of time and, on the theoretical assumption that these microorganisms at that site may be more difficult to eradicate than they are in the pharynx, have suggested that much larger doses of penicillin should be used for a longer period than recommended above. Unless further studies indicate the contrary, however, it is probable that the dosage schedules given above are adequate.

Prevention of Recurrences of Hemolytic Streptococcal Infection: Once having eliminated any hemolytic streptococci which may have been present it is essential to prevent their return, and for this also several methods are available: (1) *Benzathine penicillin G* may be given intramuscularly in doses of 1,200,000 units every four weeks; (2) *sulfadiazine* may be administered once daily by mouth in doses of 0.5 Gm. for small children and 1.0 Gm. for children and adults weighing 45.4 kg. (100 pounds) or more; or (3) oral *penicillin* may be used in doses of 250,000 units twice daily, preferably a half hour before breakfast and supper. In this connection it must be borne in mind that whereas sulfadiazine is quite effective in preventing hemolytic streptococcal infections, it is a bacteriostatic and not a bacteriocidal agent and hence is not to be relied on to eliminate hemolytic streptococci already present. Opinion varies as to which of the various methods is preferable, but all are entirely satisfactory provided the patient can be relied upon to take the medication every day without fail. If the latter is not the case, the use of benzathine penicillin G has the great advantage that it can be given by the physician himself, at four-week intervals, with assurance of protection during the intervening periods whether or not the patient is dependable. These procedures will be considered again in the discussion of the prevention of rheumatic fever.

Antirheumatic Agents: The various antirheumatic drugs (*salicylic acid, sodium salicylate, acetyl salicylic acid, neocinchophen, phenacetin, amino-*

pyrine, phenylbutazone, etc.) are powerful antipyretic and analgesic agents which, in adequate doses, effectively reduce the fever and discomfort of a wide variety of diseases. In addition, they have an anti-inflammatory action which is especially marked in the polyarthritis of rheumatic fever; but, in contrast to the dramatic benefit to the inflammation about the joints, opinion in the United States has been almost unanimous that the antirheumatic drugs are of little benefit to the inflammation of carditis. During recent years, however, the careful evaluations which have been made of cortisone and corticotropin have led also to reappraisal of the salicylates as possibly useful in rheumatic carditis because, in controlled therapeutic trials,[7] patients receiving acetyl salicylic acid have shown responses similar to those receiving the hormones. Some investigators, including the author,[12,13] have hoped since 1952 that these results meant that all three agents might be exerting an important beneficial effect on carditis. Further experience, however, makes it probable that the reverse explanation is the correct one, and that none is very effective.[14]

Corticosteroids and *corticotropin*, as noted earlier in this chapter, are now considered to be merely extremely powerful anti-inflammatory agents so far as their beneficial effects in rheumatic fever are concerned. Nevertheless, because of the particular interest in them, they warrant separate consideration in this discussion. Unfortunately, the early hope that these agents could control carditis as well as polyarthritis and pyrexia in rheumatic fever has greatly dimmed, although opinions vary as to the extent of their usefulness. Many authors[15–18] have reported promising results in controlling the valvular damage caused by rheumatic fever. Others, on the contrary, found little evidence of superiority over aspirin. Included in the latter category is the exhaustive and rigidly controlled cooperative clinical trial of ACTH, cortisone and aspirin, previously referred to, which was carried out jointly by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association.[7] In this study of 497 children, it was concluded that "there was no evidence that any of the three agents used resulted in uniform termination of the disease and on all treatments some patients developed fresh manifestations during treatment" and "at the end of one year there was no significant difference between the three treatment groups in the status of the heart." In that study, cortisone had been given over a six-week period in doses gradually diminishing from 300 mg. to 50 mg daily. Because of the possibility that the dosage schedule and period of treatment were too small the study was repeated on a lesser scale, using prednisone in doses three to four times the equivalent of those used in the "cooperative clinical trial" for a period twice as long. A control group received aspirin in doses sufficient to give a blood level of 25 to 35 mg. per 100 ml. for an equal period of time. Only *children with clinically definite carditis in whom treatment was started* within three weeks of onset of their first attack of rheumatic fever were included in the study. The results in twenty-four children receiving prednisone and twenty-three children receiving aspirin gave no support to the

view that corticosteroids in large doses over a twelve-week period have any superiority over aspirin in terms of the incidence of residual valvular damage at the end of one year of follow-up.

That there should be differences of opinion regarding the value of corticosteroids in rheumatic carditis is scarcely surprising in view of the similar differences as regards effects on such easily observed and measurable lesions as subcutaneous nodules. Some authors have reported rather rapid disappearance of nodules in patients given corticosteroids and corticotropin, whereas in the cooperative clinical trial,[7] new nodules were observed to appear, and the rate of disappearance was about the same, in each of the three treatment groups. There was no completely untreated group of patients in that study, but previous experience indicating that salicylates do not affect rheumatic subcutaneous nodules is so well documented that the results of the cooperative trial leave little reason to expect any very significant effects from the more powerful antirheumatic agents either.

How then is one to explain the differences between the dramatic benefit from salicylates and corticosteroids in rheumatic polyarthritis and the questionable effects in carditis? The answer probably lies in the predominant type of inflammation in each of those manifestations. In polyarthritis the inflammatory reaction is of the acute, exudative type, which is extremely responsive to all the antirheumatic agents. In carditis and in the subcutaneous nodule, on the other hand, the acute exudative phase usually is minor and transient, and the predominant lesion is a granulomatous one on which those agents exert less influence. Nevertheless, both *corticosteroids and salicylates may be of special value in pericarditis* where the role of acute exudative inflammation is greater, and one may hope that they are of some benefit in most patients with carditis if used early.

The possible value of giving corticosteroids and salicylates together is a question of some practical importance. Some investigators believe that salicylates act by stimulating the adrenals to put out more intrinsic hydrocortisone. Obviously if this view is correct there would be no point in administering both corticosteroids and salicylates simultaneously. The best evidence, however, indicates that salicylates do not act through adrenal cortical stimulation; hence, there is logic in using both agents at the same time.

Plan of Treatment with Antirheumatic Agents: In view of the many gaps in knowledge it is not possible to make dogmatic statements as to treatment, but on the basis of the best current information it is possible to suggest the following regimen as a reasonable approach. These measures should be started coincidentally with intensive penicillin therapy as outlined earlier.

1. In polyarthritis without evidence of carditis salicylate alone probably is preferable. Ideally, doses sufficient to give a blood level of 25 to 35 mg. per 100 ml. should be given. It is seldom necessary, however, to control dosage by checking the blood level, and rule-of-thumb schedules are sufficient. A useful formula is to give a total daily dose of 60 mg. (1 grain) per pound of body weight or 10 Gm. (150 grains), whichever is less, for the first two days; 40 mg. (⅔ grain) per pound on the next five days; and

then 30 mg. (½ grain) per pound as long as may be required. These daily amounts may be given in divided doses every four hours for the first two days and every six hours thereafter.

2. In the presence of carditis, it is suggested that prednisone (or other corticosteroid in equivalent amounts) be given in addition to the salicylate. Doses of 10 mg. of prednisone four times daily may be given for ten days, after which the total daily dose may be reduced at the rate of 2.5 mg. daily. It is recommended that salicylate be continued after the cessation of corticosteroids as long as fever, symptoms, erythrocyte sedimentation rate, and C-reactive protein (or other acute phase reactants) indicate persistence of active carditis. Furthermore, because of the theoretical possibility that corticosteroid therapy might enhance latent hemolytic streptococcal infection, it is suggested that penicillin be given in the usual doses (as described under Prevention) but twice as often so long as the corticosteroid is being administered.

Not infrequently a transient flurry of increased disease activity, as manifested by fever and increased erythrocyte sedimentation rate sometimes accompanied by mild symptoms, the so-called rebound phenomenon, *is experienced as the corticosteroid dosage reaches a low level or is stopped.* This phenomenon may occur after withdrawal of salicylate also, but less often. If, instead of being merely transient, the evidences of rheumatic activity continue or increase longer than a week, many authors recommend a second or a third course of corticosteroid. It must be emphasized, however, that current data do not indicate that such a procedure prevents ultimate cardiac damage

This discussion of corticosteroids may be closed with a brief statement regarding the undesirable effects of corticosteroid and salicylate therapy The very real hazards of long-continued, large doses of corticosteroids and corticotropin are well known. However, in the doses which have been recommended it is unlikely that anything more disturbing than transient "mooning" of the face is apt to occur. Salicylates in the doses recommended may rarely give rise to nausea, tinnitus or, in young children, hyperventilation If these should occur, two or more doses should be *omitted*, depending on severity of symptoms, after which therapy should be resumed at a lower dosage level

Rest· Physical and mental rest are of the greatest importance, but may be interfered with by pain, dyspnea, and anxiety. Much can be accomplished by skilled nursing care and by reassurance. Cardiac pain occurring in carditis often is helped by an *ice cap applied to the precordium*, but if this is not adequate, *codeine* should be given in doses large enough to give relief. If smaller doses are insufficient, 0 03 Gm (½ grain) of codeine sulfate can be given every three or four hours even to a child of five or six years of age. It is rare that morphine is needed.

Digitalis and Other Cardiac Drugs. In the presence of auricular fibrillation or congestive heart failure, digitalis is indicated in carditis just as it is in the treatment of those disorders under any other circumstances. The drug does not help the carditis itself, however. A satisfactory method is to give an initial dose of 4 U.S.P. units (0 4 Gm. or 6 grains) and then 2 U.S.P.

units (0.2 Gm. or 3 grains) morning and night until a therapeutic effect or the earliest symptoms of digitalis toxicity appear. Thereafter, 1 unit daily will usually suffice as a maintenance dose.

Mercurial diuretics may be needed also if heart failure is severe. Their use and dosage are discussed on page 309.

Diet: There is no particular diet of value in the treatment of carditis. During the acute phase the patient is often too sick to care much about food and should not be forced to eat. Light foods, especially in liquid form, will suffice during the first few days, by the end of which time the patient's appetite usually demands more. In the presence of edema from heart failure, fluid and salt intake should be limited.

Pericarditis: The treatment of pericarditis deserves special comment because of the danger of cardiac tamponade if the pressure from the accumulating effusion becomes too great. Usually no special treatment is required but *pericardial paracentesis should be done if dyspnea becomes* severe and especially if there is a sudden fall in blood pressure. In adults the anterior approach may be required but in children paracentesis can be more easily done by the posterior approach.

Treatment of Subacute and Chronic Carditis: In general the treatment of subacute and chronic carditis is the same as that of acute carditis. There are, however, certain features which warrant special mention. If the possibility of the hemolytic streptococcal carrier state has not already been eliminated by appropriate treatment, *penicillin* should be administered in sufficient amount to do so as already described. Similarly, prophylactic *penicillin* or *sulfadiazine* should then be started to prevent the return of such infection. *Salicylate* should by all means be given although present evidence indicates that damage already sustained will not be reversed and there is little evidence that the granulomatous type of inflammation present during these stages will be appreciably influenced by antirheumatic therapy. It is probable that any benefits that might result from corticosteroids or corticotropin at these stages of the disease are too doubtful to warrant their use in view of their potential hazards when given over long periods.

Rest remains the most important part of treatment although the doctrines of early ambulation and rehabilitation have questioned the advisability of maintaining complete bed rest until all signs of active carditis have subsided, which has been insisted upon in the past. One should strive for the greatest possible rest for the patient as long as evidences of carditis persist short of having the patient develop an anxiety state, and bearing in mind that some patients will obtain greater rest if permitted to sit in a chair a few hours a day than they will fretting in bed. As a guide in helping decide when graded ambulation may be started, one may rely on certain criteria. These are (*a*) normal temperature, pulse, and *leukocyte count for ten consecutive days in the absence of antirheumatic* drugs; (*b*) freedom from all manifestations of active rheumatic fever such as joint pains, erythema marginatum, and subcutaneous nodules; (*c*) normal atrioventricular conduction time; (*d*) erythrocyte sedimentation rate close to normal limits; (*e*) a satisfactory weight curve; and (*f*) good general condition. When recovery has advanced to this point the patient

should be allowed an increasing amount of physical activity daily until more or less normal life has been resumed.

The importance of doing everything possible through occupational therapy and the principles of rehabilitation to prevent the patient from becoming too concerned about his heart must be emphasized. Also the physician must consider the patient's future capacity for work. School programs for children and retraining for a more suitable occupation in the case of some adults with severe cardiac damage can begin while the patient is still in bed

Diet also plays an important role in treatment of subacute and chronic carditis as part of the general supportive care of the patient. A varied diet rich in protein is indicated and on largely empirical grounds supplements of vitamins A and C are often advised. During a long period of comparative inactivity in convalesence it frequently is necessary to limit caloric intake to prevent too great a gain in weight.

Supplementary medication is indicated as in any other diseases for the treatment of individual symptoms and complaints. Constipation resulting from the prolonged inactivity may need attention. More important is the anemia which so commonly accompanies persistent low-grade rheumatic inflammation. *Ferrous sulfate*, 0.3 Gm. (5 grains), t.i.d. after meals may be given. Very rarely, if anemia is severe and the patient's general condition poor, it may be helpful to give one or two small *transfusions* of whole blood.

Specific Therapy: In the past, various antiserums and vaccines and convalescent serum have been tried but without success. Today *antibiotics constitute specific therapy against the causative* hemolytic streptococcal infections.

Eradication of Foci of Infection: The removal of tonsils and other possible foci of infection has been widely used, although the best evidence has indicated that once rheumatic fever has made its appearance tonsillectomy does not lessen the likelihood or severity of cardiac damage. Certainly, in the light of modern knowledge, *penicillin* provides a far surer and safer means of eradicating foci of hemolytic streptococcal infection, although, theoretically, there may still be a place in rare instances for tonsillectomy if deep-seated hemolytic streptococcal infections cannot be eliminated by very intensive administration of penicillin.

Treatment of Inactive Rheumatic Heart Disease: As has already been said, patients with rheumatic heart disease in the inactive stage may have *no symptoms at all or varying degrees of diminished cardiac reserve up to* frank failure at rest. Those without symptoms require no treatment even in spite of obvious physical signs of valvular damage. They should return to the physician for periodic examinations, however, every six to twelve months and every possible measure should be taken to help them avoid reinfection with hemolytic streptococci (see under Prevention, page 166). If there is no diminution of cardiac reserve, physical activity should not be limited with the exception of the heaviest labor and the most strenuous sports. Particular care must be taken in the case of introspective patients at the periodic examinations to prevent the development of anxiety states.

On the appearance of signs of congestive heart failure or gross arrhythmias, treatment is like that of heart failure or similar arrhythmias from any other cause (*q.v.*). In addition, the patient must be closely observed for evidence that a new attack of carditis has occurred and in the event that it has, treatment is that of carditis.

Prevention: The all-important aim in the prophylaxis of rheumatic fever is the prevention or prompt eradication of the hemolytic streptococcal infections which are the inciting factor of the disease. Rheumatic patients must be made to understand the serious significance of these infections to them and, on the positive side, the protection given by faithful adherence to the prophylactic regimen. There are two important parts to this regimen: (1) The prevention of hemolytic streptococcal infections, and (2) the rapid elimination of such an infection if it should occur.

Prevention of Hemolytic Streptococcal Infections: This has already been outlined in the discussion of treatment. As noted there, *penicillin* or *sulfadiazine* daily by mouth or long-acting depot penicillin (*benzathine penicillin G*) intramuscularly every four weeks is effective. The essential factor in determination of which of the two methods to employ is the dependability of the patient, for, with the methods based on oral administration, protection can be lost if the medication is missed for a few days.

The length of time the preventive regimen should be continued is the subject of some debate. Statistical analyses indicate that the longer a patient goes without a new attack the less likely he is to have one. It is true also that attacks are apt to be less common and less serious after the age of twenty For these reasons, some authors have suggested that prophylaxis need be continued only for five years or up to the age of eighteen or twenty. However, the appearance of new attacks following cessation of prophylaxis in patients who have been successfully protected for years has occurred so frequently that it is no longer justifiable to follow such a schedule and the only safe plan is to continue prophylaxis more or less indefinitely until such time as new knowledge may permit a more definitive answer to this question.

Rapid Elimination of Hemolytic Streptococcal Infections: More recently[19] it has been shown that intensive therapy with penicillin sufficient to eliminate the carrier state can effectively prevent rheumatic attacks following a hemolytic streptococcal infection provided treatment is started within a few days. Indeed, such measures are worthwhile even up to ten days after the onset of infection.[20] The methods of administering the penicillin are outlined under the discussion of eradication of the hemolytic streptococcal carrier state (see page 160).

In spite of the effectiveness of this means of preventing rheumatic fever it cannot be relied on alone because of the frequency with which hemolytic streptococcal infections can occur in rheumatic subjects without the knowledge of the patient. It must be emphasized, therefore, that chief reliance must be placed on continuous prophylaxis throughout the year, and that this additional safeguard be thought of as a second line of defense to be employed if, in spite of continuous prophylaxis or due to a break in it, a hemolytic streptococcal infection should occur.

Other Preventive Measures: In the past, various other measures such as tonsillectomy, climatotherapy, and vaccines have been attempted. Tonsillectomy and removal to warm, dry climates have some value but probably only through lessening the likelihood of hemolytic streptococcal infections. Now *penicillin* and *sulfadiazine* provide much surer protection and, therefore, these other measures are of chiefly historical interest.

It is theoretically possible that effective protection by means of vaccines against hemolytic streptococci can be afforded and efforts are being made to prepare suitable antigens. As yet no effective vaccine is available.

Finally, the value of good general hygienic conditions in the prevention of rheumatic fever must be mentioned. The relative infrequency of rheumatic fever among the well-to-do compared with its incidence among the indigent points to the role that poor housing, overcrowding, and malnutrition play in this disease. Hence, slum clearance projects and similar sociological advances can be expected to do much to reduce the attack rate of this serious disease.

Prognosis: *The prognosis of rheumatic heart disease must be considered* separately for the immediate attack and the ultimate outcome.

The Immediate Attack: Fortunately, mortality in rheumatic heart disease is low for the first attack and has been variously reported as from 1 to 4 per cent.[4] In the past, a hyperpyrexic type of rheumatic fever was described as an important cause of death, but this type is now rare and death, when it occurs, is due primarily to carditis. In general, subcutaneous nodules and pericarditis indicate a serious type of disease. On the other hand, this is not invariably so, for occasional patients with these manifestations recover without any residual signs of cardiac damage.[4]

Ultimate Outcome: It is because of the tendency for a patient who has once had rheumatic fever to have repeated attacks that the ultimate prognosis has been so poor in the past. Fortunately, many patients with rheumatic fever recover completely. Thus, among 683 children with rheumatic fever, 30 per cent either showed no evidence of cardiac disease at any time or developed signs which subsequently disappeared.[21] On the other hand, the prognosis is less favorable once rheumatic heart disease has become established. In a group of 3129 patients with rheumatic heart disease observed until death, the mean duration of disease was thirteen years, and 50 per cent died within nine years of the onset. Twenty-five per cent, however, lived more than seventeen years and 10 per cent more than thirty years.[21]

The reason why some patients suffer serious and repeated attacks of rheumatic fever while others escape with little or no damage is hidden in the same obscurity which surrounds the pathogenesis of the disease in general. Certain factors warrant brief discussion.

Age: The age at onset of rheumatic fever has been shown to be important, for the disease tends to lead to more serious cardiac damage in children than adults.[4,22]

Sex: There is no appreciable difference in life expectancy between the two sexes.

Type of Manifestation: It has already been noted that subcutaneous nodules and pericarditis presage a serious type of disease. Chorea, on the other hand, is least apt to be associated with serious carditis.[22] In a group of children followed six years or more, the incidence of permanent cardiac damage was 18.6 per cent in those with chorea compared with 72 per cent among children with other manifestations of rheumatic fever.

Auricular Fibrillation: This arrhythmia is of serious significance in its permanent, although not in its paroxysmal, form. It has been claimed that 34 per cent of rheumatic cardiac patients die within one year of the onset of permanent auricular fibrillation and 75 per cent within three years. Some patients, however, live many years.

Severity and Frequency of Attacks: As would be expected, life expectancy is shorter for patients with severe and repeated attacks of carditis.[22] On the other hand, it must be realized that severe cardiac damage can occur in patients whose symptoms are so mild that they scarcely realize they are sick until the heart disease is far advanced.

Happily, one may close a discussion of rheumatic heart disease on an optimistic note, for the modern measures to prevent attacks in subjects of known susceptibility bid fair to change the figures on ultimate prognosis given above. Since the outcome of the first attack of rheumatic fever usually is not serious, the present means of preventing future attacks have entirely changed the previous serious prognosis. One may conclude with considerable confidence that if modern preventive measures are faithfully adhered to, the life expectancy of the great majority of rheumatic cardiac patients who have not already suffered severe heart damage should be close to normal.

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WILLIAM DOCK, M.D.



Bacterial Endocarditis

Prior to 1944, of the patients who grew up with congenital heart defects, or with valves scarred by rheumatic fever, nearly one out of four died with bacterial endocarditis. Under this term are included a variety of clinical manifestations and nearly a score of etiological entities which have as a common feature thrombotic vegetations and ulcerations of the endocardium and valves of the heart. In addition to such clinical cases, there were many lesions demonstrable at autopsy which were of no clinical importance, for the bacterial invasion of the heart was merely a terminal event, either an acute endocarditis complicating overwhelming sepsis and pyemia, or a subacute lesion developing in the final phase of a wasting disease such as cancer, uremia, or tuberculosis. Cases in which the endocardial lesions determine the clinical manifestations are grouped into acute or subacute forms, the former causing a severe febrile illness measured only in days or a few weeks, the latter smouldering on for months and perhaps afebrile for much of the time. These subdivisions are arbitrary and the course of subacute cases may be cut short by embolic accidents or congestive heart failure.

Historical Note: *The history of endocardial vegetations goes back to the* days of the early anatomists, when even postmortem clots were thought of as interesting polyps. The relation of rheumatic fever to endocardial damage was clear to English and French clinician-dissectors by the dawn of the nineteenth century, and bacterial endocarditis was recognized in the first years of the era of bacteriology By 1900 all of the commoner forms and their complications were well known to pathologists and internists, although, as with infarct of the myocardium, the diagnosis was not often made in clinical circles, especially in the milder and subacute forms. Schottmüller and Libman were largely responsible for emphasizing and making clear the nature of subacute bacterial endocarditis, and Lohlein and Baehr for recognizing the high incidence and specific character of the accompanying glomerulonephritis. Libman also brought to attention cases of febrile subacute endocarditis which are bacteria-free throughout their course. While the study of therapy has been continually and energetically pursued, both in the clinic and in the experimental animal, until 1944 it had not produced a satisfactory management for a disease which now is correctly recognized in more than 80 per cent of our hospital cases by the student clinical clerk who first takes the history and examines the patient Since 1944, the mortality has been reduced from nearly 100 per cent to less than 15 per cent, thanks to penicillin and streptomycin.

Etiology: About twenty varieties of microbes have been isolated from lesions of the endocardium. Streptococci of many types predominate, other cocci of all sorts are not infrequent, while the bacilli range from tubercle and influenza, to diphtheroids, virulent diphtheria organisms, Brucella, Eberthella, Salmonella, Klebsiella, Pseudomonas, and others. With most of the rare types, implantation on the heart valves or the endocardium of the walls is merely an unusual complication of the illness usually caused by the specific bacterium. A case of pneumonia is complicated by or followed by pneumococcus endocarditis or a gonorrheal urethritis is followed by gonococcal lesions on the heart valves, and the new disease thus established overshadows that from which it developed. In a few cases due to nearly all these organisms, and in most of those due to the nonhemolytic streptococci, no febrile illness precedes the manifestations of bacterial endocarditis, which seems to strike "out of the blue."

The infections with gonococcus and meningococcus rarely run a slow subacute course, those due to nonhemolytic streptococci and the influenza bacillus only occasionally are acute, but it is incorrect to consider subacute or slow endocarditis as synonymous with Streptococcus viridans endocarditis. The sharp lines drawn on the basis of etiology cut across the vague and arbitrary borders of acute or subacute types of disease. Various types of the Streptococcus viridans (that is, aerobic streptococci which cause minimal hemolysis, but some change in color of hemoglobin; alpha type streptococcus) dominate the bacteriology of this disease because they occur in two-thirds of the clinical cases, and because they were present in most untreated cases in blood cultures taken over months. Per week of clinical endocarditis, the nonhemolytic streptococcus is probably ten times as frequent as any other organism or even all others together. Occasionally, nonhemolytic (gamma type) streptococci, which cause no discoloration of hemoglobin and may be anaerobes, are the infecting agent. These are considered as enterogenous infections, since such organisms are normally present in the bowel.

Acute lesions due to pyogenic cocci affect less than 3 per cent of patients whose hearts or great vessels are the seat of congenital or rheumatic disease. On the other hand, such lesions cause the dominant clinical features of the final illness of 0.2 to 0.4 per cent of patients coming to autopsy without congenital or rheumatic heart disease, and in such cases the right side of the heart is not infrequently involved. Thus, acute bacterial endocarditis is clinically most often seen in patients who have had no previous heart disease; it is favored by fibrotic lesions, but virulent organisms are by no means dependent on such chronic disorders for the opportunity to invade the heart.

Quite different is the situation with regard to the subacute cases, most of which involve the left side of the heart and are due to nonhemolytic streptococci. About one-third of the cases of congenital heart disease surviving into childhood,[1] and one-fifth of the cases of chronic rheumatic valvular disease will have this complication eventually. Chronic lesions, on which the subacute bacterial disease is engrafted, are grossly demonstrable in four out of five cases, and careful histologic study proves that fused

ic cusps or unimposing rheumatic scars are present in most of the rs. Those with normal valves are more likely to have acute than ›tococcal endocarditis. Thus, in subacute lesions the soil is the most ›rtant consideration etiologically, and the organisms which flourish in altered tissue are the streptococci which are commonly present in the th and gut. They probably enter the blood stream of "normal" people ıowers associated with such frequent incidents as colds, acute gastro- ritis, tooth extractions, tonsillectomies,[2] pelvic infections in both sexes, even with no clinical symptoms of any sort. The toothbrush probably tches these organisms into the gingival veins and lymphatics, and not f them are disposed of before reaching the left ventricle. In acute endo- itis, the virulence of the organisms, and the effects of their toxins in ring the endocardium are more important than the "soil," which may ıay not have been prepared by previous disease.

'hile infected emboli, lodging in the vessels which are present in scarred es or beneath the endocardium, are a potential cause for these lesions, ›ems certain that the valvular lesions at least are due to lodgement of :eria in the minute platelet thrombi which occur along the lines of ure of the valves, or at places where defects cause unusual stream or tissue friction. Such bland thrombi are most frequently found on es altered by sclerotic or fibrotic lesions, and where there are such con- ital defects as fused aortic cusps, patent interventricular septa or a tus arteriosus. Similar vegetations may occur in arteriovenous fistulae. ›se bland thrombi are more likely to form when the endocardium is ıred by nutritional defects, toxemia, or wasting disease. Such thrombi usually only of microscopic dimensions, but they may form fine etations and such small sterile warty lesions are far more common, in ting diseases, than terminal subacute bacterial endocarditis. The sites ›re these sterile and minute thrombi form are also the favored sites for terial endocarditis.

)nce the latter disease is established the blood stream constantly con- ıs organisms and small thrombi, and if valves were normally vascularized ›avalvular emboli would soon set up progressive lesions of all four ›es. As a matter of fact the disease is usually found on all scarred ves in the old rheumatic cases, and only on one if the others are free of otic change. "Kissing lesions" at points where two leaflets touch, and ead along lines of closure are common findings, but evidence for em- ic invasion of valves is absent even when embolic lesions are numerous skin, viscera, the brain, and, as mycotic aneurysms, in the walls of ar- :es. While the lesions are occasionally confined to the walls of the ırt (parietal as contrasted with valvular endocarditis), it is remarkable .t the large mural thrombi which follow myocardial infarcts rarely become ›cted. Cases in which syphilitic lesions have prepared the soil for bac- ial endocarditis are also uncommon.[11] In elderly patients ulcerated ›rotic lesions occasionally become the seat of bacterial endocarditis, but ıny of the cases are not clinically significant, being terminal infections of :ients severely ill from other causes.

Etiology: About twenty varieties of microbes have been isolated from lesions of the endocardium. Streptococci of many types predominate, other cocci of all sorts are not infrequent, while the bacilli range from tubercle and influenza, to diphtheroids, virulent diphtheria organisms, Brucella, Eberthella, Salmonella, Klebsiella, Pseudomonas, and others. With most of the rare types, implantation on the heart valves or the endocardium of the walls is merely an unusual complication of the illness usually caused by the specific bacterium. A case of pneumonia is complicated by or followed by pneumococcus endocarditis or a gonorrheal urethritis is followed by gonococcal lesions on the heart valves, and the new disease thus established overshadows that from which it developed. In a few cases due to nearly all these organisms, and in most of those due to the nonhemolytic streptococci, no febrile illness precedes the manifestations of bacterial endocarditis, which seems to strike "out of the blue."

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coccal endocarditis. They had many organisms in the vegetations, demonstrable by culture as well as on direct examination after death. These organisms were often close to the surface or on the surface of the vegetations, and not simply buried in its depths. Their failure to grow from the blood merely shows what high bacteriostatic properties the blood possessed, and how ineffective this was in arresting the disease or acting on organisms in the thrombi. Nevertheless, a few untreated patients with acute and subacute endocarditis occasionally became free of bacteria, and completely healed scars were found at autopsy, often with no history of an illness recognizable as bacterial endocarditis.

Incidence: Clinically recognizable cases occur from childhood to senility, but there is a sharp peak in incidence between puberty and the early forties. In older people the anatomical incidence is still high into the sixties, but many of these either are terminal lesions in other fatal illnesses, or are of brief clinical duration, dominated by embolic phenomena which can scarcely be distinguished from the vascular accidents due to degenerative disease. Bacterial endocarditis singles out the well-compensated cases of healed rheumatic heart disease, and the functionally unimportant congenital lesions. When patients with heart disease decompensate they often have marked malnutrition and obvious damage to the respiratory and digestive tracts. Yet such patients, even when in miserable physical condition, retain a remarkable resistance to bacterial invasion of the heart. Even in cases of auricular fibrillation without congestive failure, bacterial endocarditis is uncommon,[15] probably because of the lessened trauma to the mitral valves when, with the abolishment of presystolic auricular contraction, the closure of the mitral valve takes place more gently and the loud, snapping, first sound becomes much softer. Severe congestive failure in cases of endocarditis may be precipitated by bacterial destruction of valve leaflets without arresting the progress of the endocardial infection, but congestive failure plays some role in preventing bacterial endocarditis, even though powerless to arrest its progress

While there are some who believe this disease is more frequent than formerly, a comparison of Harbitz's report (Norway, 1886-96; 1700 autopsies)[5] with that of Ophuls (California, 1900-1923; 3000 autopsies) and with our own records for California (1934-38; 2300 autopsies) indicates no striking change in relation to total autopsies or to chronic rheumatic heart lesions over a period of fifty years and from 36 to 60° north latitude. Clinical recognition is more frequent, and each case is probably seen by a larger number of physicians than in the early decades of the history of the disease. Marked variations in annual incidence may have occurred in some localities, as suggested by Musser[12]

Recognition: Few diseases assume so varied a clinical course or conceal their true nature more completely behind some sequel appearing to be an unrelated disorder. Yet the untreated disease followed this pattern: A young or middle-aged person gradually notices a constant disinclination for food, work and play, and may be aware of fever, irregular or occurring in the afternoon He (or she, since the disease is almost as frequent in women) may be unaware of any heart lesion, or may have almost forgotten

the diagnosis made on some prior occasion; at any rate, cardiac symptoms do not obtrude on his consciousness. Tenderness or clubbing of finger tips, or petechial lesions may be noted by the patient. He may finally take to bed on his physician's orders, rather than because he feels quite unable to be up. Thus begins a steady failure, not unlike that of phthisis or neoplastic disease, but complicated toward the end by embolic accidents—palsies, abdominal pain, acute bowel obstruction, pain and loss of function in arm or leg. There is usually anemia, a normal or moderately elevated white blood count, rapid sedimentation of blood, slight proteinuria, rarely purpura due to thrombocytopenia.

The distinctive features which suggest the diagnosis are the auscultatory abnormalities in the heart, a slight splenic enlargement, clubbed fingers, petechiae, and red cell casts or an abnormally large number of red cells in the urine. The latter may be demonstrable only when timed urine specimens are examined under constant conditions, and the auscultatory findings may not be very striking—merely a systolic murmur somewhat harsher than is to be expected of a functional murmur due to fever. If there are definite diastolic murmurs, or a basal systolic thrill, the existence of an organic lesion and its probable relation to the febrile illness are at once apparent.

In some cases where only an apical systolic murmur is first evident, one must have the patient lie supine and *a little on the left side while listening at the apex and about the apical region, in order to hear a diastolic or presystolic murmur.* Or it may be revealed when the pulse is slowed by pressure on the carotid bulb. The murmur of mitral stenosis, especially in this group of patients, often is difficult to detect, but repeated search under various conditions serves to prove that some of the harsh systolic murmurs or very sharp, loud, first sounds have a diastolic element associated with them. Repeated search for conjunctival and buccal petechiae, as well as for those on the skin, and the observation of clubbing of the fingers must also be stressed in the physical examination.

Normal heart size and normal roentgen contours do not rule out bacterial endocarditis, but slight cardiac enlargement and abnormal contour, like a harsh systolic murmur, may suggest or confirm the diagnosis of organic heart disease on which bacterial infection might be superimposed. The constant search for petechiae, the repeated and painstaking examination of urine for red cells, and of the abdomen for splenomegaly are of particular importance *when the blood cultures are negative, as is true in about one of eight cases carefully studied over long periods of time*, and in a larger proportion of cases when casual use of antibiotics has preceded the blood cultures. When the cultures are negative, embolic phenomena, petechiae, glomerulonephritis, and splenomegaly, in various combinations, sooner or later serve to confirm the diagnosis suggested by fever and auscultatory abnormality.

While these classical cases, with or without positive culture, are usually suspected on first examination and proved within a few days, the others may for weeks escape detection even by the experienced diagnostician, and the patients die before the condition is recognized. Some of the pitfalls are best

emphasized by contrasting cases of bacterial endocarditis with other types of disease with which they may be confused. The following cases were seen before the era of penicillin, and show the natural course of the disease:

Severe Gonococcal Arthritis; Bacterial Endocarditis; Erroneous Diagnosis of Coronary Thrombosis: A widow of fifty-two developed polyarthritis with fever at times. After several months she suddenly had substernal distress and congestive heart failure, with pulmonary edema and hepatic tenderness. The heart sounds were muffled and the rate about 150 when she was brought to the hospital; no definite murmur was recognized. She died within three days of the cardiac accident, and at autopsy was found to have a mild endocervicitis, and gonococcal endocarditis with destruction of one entire aortic leaflet.

Comment: A genteel social position and the relatively benign course of the polyarthritis clouded the recognition of gonococcal infection; the stormy onset of cardiac symptoms suggested myocardial infarction; in severe heart failure, with rapid rate and gallop sounds the diagnosis of valve lesions is particularly difficult.

Pneumococcal Endocarditis Mistaken for Empyema: A man of fifty-six had a severe and prolonged bout of pneumonia, probably bronchopneumonia although rather extensive in the right upper and middle lobes. The temperature never fell to normal, but began to fluctuate in the second week after a few days in which it rose only to 37.5° C (99.6° F.). The roentgen examination still showed haziness on the right, and though there were no definite physical signs, thoracentesis was repeatedly attempted. A systolic murmur, heard throughout his illness, became more harsh, the heart shadow larger. Blood culture, positive for pneumococcus, was obtained on the day of death; the mitral valve was the seat of many cauliflower-like vegetations, and many chordae tendinae were broken.

These examples, taken from cases of rapidly progressive endocarditis due to other organisms than Streptococcus viridans illustrate certain diagnostic difficulties. The following case, due to Streptococcus viridans, shows that rapid progress, or acute endocarditis, may be due to that organism as well as to those usually considered far more virulent.

Onset of Endocarditis Simulating Typhoid Fever: A man of thirty-two was on his vacation in the country, and at the end of three weeks began to have headache, anorexia, and prostration. Fever was noted on two evenings, and he returned to his home city, entered a hospital. He was apathetic, had a fever which ran between 39° and 39.8° C. (102° to 103.5° F.), but a pulse rate of 100. There was a rather harsh systolic murmur in the pulmonic area, which the patient knew had been noted many years before. The white count was 6800, blood culture and Widal, negative. The spleen was palpable two days later, but on the fifth day a second culture yielded many colonies of Streptococcus viridans. The patient was taken to his home, died in less than a month of the onset of symptoms. There was no autopsy. The diagnosis was patent ductus arteriosus; bacterial endocarditis.

In this case toxemia was more marked and the clinical duration shorter than in many cases of meningococcus or gonococcus endocarditis. Today, such a case would be treated by ligation of the ductus and with penicillin.

Undiagnosed Endocarditis; Hemiplegia: In a girl, aged eighteen, latent glomerulonephritis with slowly rising blood pressure was followed for three

years; at twenty-one the pressure was 140/100; blood urea, 50. The patient had a tooth extracted and next day had nausea, headache, blurred vision She felt achy and ate poorly; three weeks after the extraction she suddenly developed left hemiplegia. On entry, two days later, there was a spastic paralysis, a loud systolic apical murmur, scattered retinal hemorrhages, blood pressure 140/80, temperature 39.8° C. (103 5° F.). There was a leukocytosis of 42,000, secondary anemia with hemoglobin, 55 per cent (Sahli). Blood urea 70 mg. per cent. She died four weeks after the tooth extraction, presumably of a cerebrovascular accident. On the mitral valve there were two small vegetations with one ulceration through the leaflet, and there were infarcts in brain, spleen, and kidney Smears of the vegetations showed streptococci in short chains.

Undiagnosed Endocarditis, Uremia. Mistaken Diagnosis of Gastric Carcinoma, or Visceral Purpura· A printer, forty-four years old, had had rheumatic fever at seventeen, and later had been refused insurance because of heart trouble. He came to the surgeons because of hemorrhoids, but he also was very thin and had bleeding gums, as well as classical signs of mitral stenosis However, the hemorrhoids were excised on March 11th, and he was seen every few weeks, to June 6th, because of rectal discomfort. On July 20th, a friend arranged to have him enter the hospital, and then it was learned he had begun to have mid-epigastric pain one hour after meals soon after the hemorrhoidectomy. For a month he had been vomiting once or more daily; the vomitus was sometimes blood-streaked. He was very weak, at times disoriented The temperature, during the six days between entry and death varied between 35 8° and 37° C. (96.6° and 98.6° F.), the pulse was 70 to 80 on entry, rising to 140 on the day of his death. His blood pressure, which was 160/90 at the time of his entry in March, was now only 110/70 There were many bruises, purpuric spots and petechiae on the skin, purpuric spots on conjunctivae and in the mouth, bleeding gums; a red count of only 2 8 M ; hemoglobin, 43 per cent; white count, 13,000; platelets, 60,000 Several examiners at this time could detect only a systolic apical murmur and discounted the surgeons' diagnosis of mitral stenosis. The liver and spleen were palpable, the liver tender, and the urine contained much protein, many red cells and white cells By x-ray a 40 per cent six-hour gastric residue and some irregularity of the first part of the duodenum were noted The heart was not enlarged, the left auricle "a little prominent" Transfusions failed to help, and he was comatose for a day before his death. The blood urea, reported after death, was 480 mg per cent At autopsy, there was a healed and calcified rheumatic mitral endocarditis, with very little stenosis; vegetations containing streptococci on one leaflet, embolism of the left coronary artery with a myocardial infarct; severe diffuse acute glomerulonephritis

It is possible that in some of these cases correct diagnosis would not have altered the outcome, although it would in one case have prevented repeated thoracentesis; in another, wearisome gastrointestinal x-ray studies and hematological investigations for purpura.

Among the conditions with which bacterial endocarditis is likely to be confused are Hodgkin's disease, bone abscess, undulant fever, pyelitis, cardiac or pulmonary infarction, meningococcemia, and many others. Rheumatic carditis and disseminated lupus erythematosus are the two conditions most often confused with subacute bacterial endocarditis. The latter may be complicated by uremia, by a cardiac infarct, or cerebral acci-

dent which overshadows the real cause of trouble; it may run an afebrile course with anemia and hepatosplenomegaly simulating cirrhosis or lymphoma. *Positive blood cultures may lead to an incorrect diagnosis* of bacterial endocarditis in cases of meningococcemia, pylephlebitis, sinus thrombosis, infected arteriovenous fistula, suppurative arthritis, and even pyelitis or pelvic vein infections.

Less common than failure to recognize an endocardial infection is an erroneous diagnosis of bacterial endocarditis when the septic focus is not in the heart, but the latter error is extremely serious since it prevents the use of therapy which might successfully combat the actual cause of the fever and bacteremia. It is not enough to be on the lookout for bacterial endocarditis and take blood cultures in all patients having fever not clearly due to some other disease; only a painstaking history and physical examination, with indicated laboratory studies, will bring to light the other *causes of bacteremia in which antibiotic therapy may fail if a suppurative* focus is not attacked directly. And such a study and careful analysis of evidence are necessary to confirm the diagnosis of endocarditis in the bacteria-free stage. Patients with bacteria-free endocarditis, if untreated, face the same unhappy outcome as those with constantly positive cultures,[3,7] and the endocarditis may be arrested by therapy.

Disseminated Lupus Erythematosus: Recognition of lupus disseminatus has been made more precise by discovery of the phenomenon of nucleoprotein-engorged leukocytes (L.E. cells) in bone marrow and in preparations of shed blood. The Snapper ring preparation and other technics have greatly increased the sensitivity and dependability of this method of laboratory diagnosis. The butterfly lesion of the face, formerly an important clue to the diagnosis of lupus erythematosus, is now known to be transient, or entirely missing, in patients having the classical renal glomerular lesion, polyserositis, and the curious endocardial vegetations on the ventricular, rather than the atrial, side of the mitral leaflets. These lesions, with peculiar arteritis, myocarditis and necroses in lymph nodes, are found in various combinations in disseminated lupus.

Such patients are treated as cardiac patients because of pericarditis, or as patients having renal disease because they have marked proteinuria, hematuria, and cylindruria with rising blood urea levels. Most often, however, their affection simulates rheumatoid or rheumatic fever, with joint pains and swellings. Leukopenia is a very common finding, and systolic murmurs at the apex, pericardial rubs, and myocardial failure are not uncommon. The disease has spontaneous remissions and exacerbations; skin lesions and fever may flare up after exposure to the sun, and subside on treatment with salicylate. Occasionally, even the most sensitive L.E preparations give negative response in the early phases of a disease, the reaction becoming positive after weeks or many months False positive serologic reactions for syphilis may precede appearance of L.E positivity. The disease is controlled by adequate prednisone or cortisone therapy, and usually flares up as the dose is decreased or cut. Some patients, however, have experienced long remissions after two to four years of control by corticoid compounds, remaining in good health with no therapy. Since the

disease is uninfluenced by antibiotic therapy, it is of great importance to exclude the possibility of disseminated lupus erythematosus when studying patients suspected of having subacute bacterial endocarditis.

Rheumatoid Arthritis with Valvular Disease or Aortitis: In rheumatoid arthritis, and especially in the patients with spondylitis (Marie-Strümpell disease), either aortitis with aortic insufficiency, or actual valvulitis leading to aortic or mitral murmurs occurs not infrequently. Usually these patients are chronically ill and sometimes afebrile when cardiac features appear, but occasionally fever, vague joint pains, leukocytosis, rapid sedimentation rate, and cardiac signs have led to the suspicion of bacterial endocarditis, and even to treatment in the absence of positive blood cultures. Films of the spine may reveal no abnormality even when backache is severe; the earliest roentgen evidence is found in the sacroiliac synchondrosis, which becomes altered and even ankylosed before the vertebral bodies show roentgen changes. In this disorder also, corticoid therapy controls the clinical features and must be sustained for months or years.

Rheumatic Fever: Although acute rheumatic fever may occur in patients with active bacterial endocarditis, and acute pyogenic invasion of valves during acute rheumatic carditis, these are extremely rare combinations, and the usual problem is to distinguish active rheumatic fever from subacute bacterial endocarditis In active rheumatic fever the antistreptolysin titer is high, and reactions to skin tests with streptococcal antigens are positive; in bacterial endocarditis reactions to these tests are usually negative.[10] Spleens are rarely palpable in acute rheumatic fever, frequently in subacute endocarditis. The temperature charts, leukocytosis, sedimentation rates, C-reactive proteins, and responses to salicylate or corticoids may be the same in both diseases, and in both there may be anemia, cardiac murmurs and roentgen changes, and latent heart failure may occur. The electrocardiogram may show abnormality in both diseases, but A-V heart block is not unusual in rheumatic carditis and is seen in bacterial endocarditis only when aortic inflammation extends into the septum. Embolic phenomena are very rare in rheumatic carditis, but purpuric lesions can occur and be mistaken for embolic lesions of mucous membranes. Clear-cut embolic phenomena or hemorrhagic Bright's disease usually mean that the condition is not rheumatic fever, and restrict the diagnostic possibilities to bacterial endocarditis and periarteritis. In the latter, eosinophilia may occur; this is very rare in bacterial endocarditis.

Types of Endocarditis: In acute bacterial endocarditis, high fever and leukocytosis, multiple hemorrhagic lesions of nail beds, skin and mucous membranes are frequent, and sudden change in murmurs with onset of heart failure follows ulcerative destruction of leaflets. The initial culture is usually positive for pyogenic organisms, and since delay in treatment is fatal, intensive penicillin treatment, by vein, is started after blood for two separate cultures has been drawn. In the subacute disease, clubbed fingers, tender spots on fingers and palpable spleen may appear, as well as petechiae on skin or mucous membranes, but repeated complete examinations are essential in order to detect these transient lesions. While most cases are due to streptococci, cultures may reveal such organisms as Hemo-

philus influenzae, coagulase-negative staphylococci, or coliform organisms.

The type of endocarditis seen by a physician depends on what sort of patients he has in his wards. In private practice, the alpha streptococcal infections exceed the usually quoted figure of 85 per cent; in municipal wards one sees more than 15 per cent of acute staphylococcal and other pyogenic invaders Among narcotic addicts using intravenous injections, involvement of the right side of the heart and unusual organisms of low virulence cause special problems in diagnosis and management.

Treatment of Patients with Positive Blood Cultures: Penicillin, in the dosage originally tested under Federal auspices—200,000 units daily for fifteen days—cured almost half of the patients having alpha streptococcal infections, but courses of ten to fourteen days now are limited to those with organisms sensitive to less than 0.5 unit per ml. The recommended course[16] is 600,000 units each six hours, with 1 gm streptomycin or dihydrostreptomycin each twelve hours for five days, 1 gm. each day thereafter. Relapse rates in patients on this regimen barely exceed 5 per cent, but many physicians prefer three- to four-week courses even for these. The adjuvant action of streptomycin, helpful in such cases, is essential with more resistant strains, and especially with enterococci, the heat-resistant Lancefield D strains.

When resistance of streptococci to penicillin is in the range of 5 to 40 units per ml, the courses are lengthened to six weeks, usually from the time fever drops under therapy, and the penicillin dose, best given by continuous intravenous infusion, is 20 million units daily. Dosage up to 100 million units daily has been effectively given in cases with high resistance. If 0 5 gm. probenecid is given every six hours, by mouth, blood levels are about doubled, and dosage can be halved. Two grams of streptomycin or dihydrostreptomycin, divided in four daily doses is given for two or three weeks, half that dose for the rest of the course. A total of 100 mg. heparin per twenty-four hours in the infusion reduces trouble due to thrombosis about indwelling plastic catheters, but anticoagulant levels of heparin are not desirable and are dangerous should cerebral or splenic infarction occur.

A special problem occurs in penicillin-sensitive patients, seen more frequently each year Desensitization, as with horse-serum-sensitive patients with diphtheria or tetanus, is usually preferable to use of less effective antibiotics. Desensitization can be accomplished by starting with 10 units intravenously, and increasing five- or tenfold every twenty minutes. Epinephrine is kept on hand for use if serious reactions occur Pyribenzamine priming and continued dosage reduce skin reactions, and corticoids also may be useful or necessary at the start of such a course. Even in patients not showing any other sensitivity to penicillin, low-grade fever is not unusual, but fortunately it comes on after the initial fall when therapy is effective, and is rarely associated with any clinical symptoms—the patients feel well and have good appetites, and the fever falls when the treatment is ended at the determined time for the type of infection. Raising dosage usually increases the fever, which must not be confused with persistent infection.

Staphylococci occur in about 10 per cent of cases of endocarditis, and only occasionally are these organisms highly sensitive to penicillin and treatment is effective with six-week courses of 40 million units a day if resistance is 0.5 to 2 u./ml.; 3 million units a day if under 0.5 u./ml.[8] Tests for sensitivity to tetracycline (Aureomycin, Terramycin and Tetracyn being regarded as entirely similar antibiotics), chloramphenicol, erythromycin, novobiocin and vancomycin must be run on strains resistant to over 2 u./ml. When the organism is sensitive to less than 2 gamma of tetracycline per ml., the average dose is 500 mg. every six hours, by mouth, for six weeks after a good clinical response to 10 mg./kg., given intravenously every eight hours, has been obtained. With chloramphenicol sensitivity to 4 gamma per ml. or less, the same schedule may be followed, but good results are reported from giving 6 gm. by mouth, followed by 1 gm. every four hours until a good clinical response is evident, then 1 gm. every six hours for six weeks. Dosage schedules for the other antibiotics mentioned should be carefully planned (vancomycin can only be given intravenously) and all these agents are given in four- to six-week courses, with maximal tolerated daily dose. Bacitracin has marked and, to some extent, irreversible nephrotoxic action and is used only with great caution when no other agent is effective. Combining heavy penicillin dosage with the bacteriostatic agents—tetracycline, chloramphenicol, erythromycin or novobiocin —is not advisable theoretically, but may prove effective in some resistant cases Bacitracin is effective with penicillin, and combinations of two bacteriostatic agents are effective.

About 5 per cent of cases of bacterial endocarditis are due to all other pyogens. Pneumococcal and meningococcal endocarditis, both often accompanied by meningitis, can be controlled by penicillin, but valvular damage quickly becomes irreversible, so that swift institution of massive therapy (4 million units/day for first week, 2 million/day for two to four weeks more) is imperative. No sensitivity tests are needed, and in suspected cases treatment should be started as soon as blood for two separate blood cultures has been drawn. In meningococcal sepsis, Dowling recommends 10 million units of penicillin intravenously the first day, with full dosage of sulfadiazine, to control meningeal invasion [8] Beta streptococcal infections also are acute and rapidly destructive, and demand similar therapy. Sensitivity must be checked, as rare enterococci are hemolytic and require streptomycin in addition. Gonococcal endocarditis responds well to the aforementioned dosage schedule, but here, too, prompt institution of therapy is necessary. Even with the best treatment, valvular damage in all these acute endocarditides is rapid and heart failure occurs in almost one-half the patients whose lesions are sterilized.

In Brucella endocarditis, sensitivity need not be tested. Two grams of tetracycline daily for four weeks, with 1 gm. streptomycin for two weeks, half that for the next two weeks, is the standard and very effective treatment.

With other infections the following sensitivity tests are in order, treatment being given for six weeks with the maximal tolerated dosage during the first days to secure clinical remission. Escherichia coli, Aerobacter and

Salmonella—tetracycline, chloramphenicol and streptomycin. Proteus—tetracycline, chloramphenicol, novobiocin and penicillin. Pseudomonas—tetracycline, chloramphenicol and polymyxin.

In alpha streptococcal infections, the death rate from heart failure, embolic accidents and other causes may be as high as 10 per cent before a course of therapy is completed, and over 15 per cent from heart failure in the first year. In the other types of infection the initial and delayed death rates are two to three times as high as in subacute streptococcal endocarditis. Because each 10 million units of penicillin has the equivalent of 1 gm. NaCl or KCl, sodium penicillin must be avoided in heart failure and potassium penicillin must be avoided in renal failure; suitable diets should be used in all such cases.

Management of Suspected Endocarditis with Negative Blood Cultures: When blood cultures are negative in patients with persistent unexplained fever, with known valvular heart disease, or with systolic murmurs and a history of recent tooth extraction, or respiratory infection, the possibility of streptococcal endocarditis with negative cultures must be conceded. If some antibiotic therapy has been given before blood cultures are prepared, the probability is increased, but even before antibiotics were used, nearly 10 per cent of patients with proved streptococcal endocarditis were bacteria-free for long periods of active febrile disease.

When blood for half a dozen cultures has been drawn, other causes for fever have been excluded, and a good temperature curve has been established, therapy may be started. I consider this wise even when petechiae and embolic lesions are absent, and the differential diagnosis suggests the possibility of Hodgkin's disease or lymphoma. The latter is incurable and does not respond to penicillin-streptomycin therapy, so it is better to start treatment on doubtful cases in the hope that the presence of the curable disease will be proved by the response to treatment.

The treatment schedule may be that recommended earlier in this section for alpha streptococci or enterococci of low sensitivity, but I prefer to start the therapy with 2 gm. of mixed streptomycin daily, and 200,000 units of procaine penicillin every six hours. If there is a prompt clinical remission, the dose is raised to one million units every six hours, and the treatment ended in three weeks. In such cases, a relatively sensitive organism presumably is present. When no clinical response is seen by the fourth day, the dose schedule of 40 million units a day is started, and if there is then a clinical remission the course is continued for six weeks, with 1 gm. streptomycin daily after the end of two weeks' treatment with 2 gm. daily.

When there is no response to massive therapy of this sort, the chance of subacute disease due to Brucella or other organisms is very small, but a trial of tetracycline and streptomycin, for Brucella, or of chloramphenicol therapy, in full dosage, is justifiable for at least one week. If that fails, and other signs of endocardial infection, particularly embolic lesions, are occurring, bacitracin may be tried. Since alpha streptococci cause more than 90 per cent of the bacteria-free subacute cases, the need for testing

other antibiotics rarely arises in the patients whose palpable spleen and embolic lesions leave no doubt about the nature of the disease.

Relapse, Recurrence, Reinfection: A cause for great concern is the problem of new manifestations of disease in a patient who has responded well to therapy. Only when the same organism, but with higher drug resistance, is recovered during or soon after the initial course of treatment can one regard this as a relapse due to inadequate dosage and development of resistance. In all such cases, a new course, usually longer as well as more intense, must be started.

When the patient remains well for three months or more, and a similar organism with similar sensitivity is isolated, one can speak of recurrence or reinfection. If a different organism is isolated, there can be no question of anything but reinfection, even if this occurs during therapy. Thus, staphylococcal infection may supervene in viridans endocarditis as a result of skin infections at injection sites. One of our patients had a relapse about one month after only three weeks of treatment with 800,000 units of penicillin daily, recovered completely with longer, more intensive treatment, but a year later had a new infection with a different and far less sensitive strain. Two years later, the patient returned with an acute endocarditis due to beta streptococcus, sensitive to 0.02 units per ml. Thus, one relapse and two reinfections were observed, all successfully controlled.

Prophylaxis: In all recovered patients, and in many well-compensated people with valvular heart lesions, prevention of bacterial endocarditis must be advised. This centers on care of the teeth, and use of penicillin whenever extensive dental work is undertaken. The usual regimen is half a million units of procaine penicillin twelve to twenty-four hours before extraction or treatment likely to cause extensive bleeding of gums, and similar doses daily until four days after all bleeding has subsided. After operations for hemorrhoids, bowel resection or prostatectomy, infection with enterococci is to be feared, and in such cases a million units of procaine penicillin and 1 gm. of streptomycin should be given every twelve hours, preceding the operation and until three days after all catheters, packs, or dressings have been removed and discharge has ceased.

It is wise for such patients never to use stiff-bristled tooth brushes, and if they have extensive caries and a progressive series of extractions seems probable, it may be wisest to extract all teeth at one time, with full prophylactic control. There is evidence that endocarditis lenta develops less frequently in the edentulous,[6] but routine extraction of all teeth is unwise. During effective therapy of an attack of streptococcal endocarditis, it is our custom to have all imminent dental or prostatic surgery completed during the second or third week of the six-week course, rather than have the patient's convalescence interrupted by further interventions.

One curious result of our attention to clearing up lesions apt to cause trouble, or already causing symptoms, has been to raise the morale of patient and family. More than any reassurance as to effectiveness of modern therapy, the physician's concern about future well-being impresses on the family and patient the fact that recovery is expected, after a good initial response to therapy. In all patients doing well, however, meticulous

attention to salt restriction or depletion, adequate and appetizing meals, examination of the sites of intramuscular injections, and care for the patient's general well-being are absolutely essential if one is to restore the maximum percentage to full recovery. Confinement to bed should be limited only to those patients who are prostrated by fever, and to the proper alternation of bed and chair in those who are afebrile so as to promote comfort and rest. Patients who sit up for meals, and even stroll a short distance to the bathroom, usually do much better than those forcibly kept on "complete bed rest."

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WILLIAM R. MINNICH, M.D.
AND
WILLIAM L. PAULLIN, JR., M.D.

9

Cardiovascular Syphilis

Introduction: Syphilitic heart disease is a term which means primarily syphilis involving the aorta. There are other parts of the cardiovascular system involved in this disease, but the aorta is the portion which is most frequently damaged and which shows the earliest manifestations of syphilitic invasion.

As early as 1728 Lancisi,[9] and in 1761 Morgagni, suspected the relationship existing between syphilis and aortic aneurysm; but the real story of syphilitic aortitis was not written until 1876, when Francis H. Welch of England described the gross and histological lesions found in this condition. Dohle, a pupil of Heller's, in 1885 wrote rather comprehensively on the subject, and in 1907 Reuter[12] and Schmorl demonstrated the *Treponema pallidum* in lesions of syphilitic aortitis. Since that time, much confirmatory evidence has been produced showing the close relationship existing between syphilis and a certain type of pathological lesion occurring in the aorta. Additional evidence of the part played by syphilis in this condition has been strengthened by the presence of a positive VDRL reaction occurring in the blood of so many patients with aortic involvement.

Etiology: The *Treponema pallidum* is the causative organism of syphilis. At the time of primary infection, the treponema enters the blood stream and is distributed generally throughout the body. Curiously enough, and for an equally unexplained reason, the entire thoracic aorta seems to be an excellent site of invasion for these organisms; they collect in the adventitia and the media and may lie seemingly dormant in this location for varying periods of time before producing signs or symptoms which would lead to their discovery. The following case history represents a rather graphic illustration of an early and disastrous lesion.

A Negro single male, nineteen years of age, was admitted to the hospital in great respiratory distress. While dressing for work, he suddenly developed marked shortness of breath and though he started to work, he was unable to continue and returned home where he remained until twelve days after the onset of symptoms when he began to notice swelling of the face and one month afterward he was brought to the emergency clinic and admitted to the hospital in a rather severe state of shock. There was a past history of sore throat at the age of seven without joint pains Seven months prior to the onset of his illness, he had gonorrhea and a penile lesion At this time, the *Treponema pallidum* was found in the exudate from this lesion

On physical examination, the pulse rate was 100, blood pressure 140 over 56 He was a well-developed Negro male propped up in bed in noticeable respiratory distress. He was cyanotic and there was definite neck vein distention, numerous moist rales were heard throughout both lungs and the heart was enlarged to the



Galen, although ignorant of [illegible]

The former, no doubt, represented the commoner type before the widespread appearance of syphilitic aortic aneurysm in 1495.



Paré, one of the greatest surgeons of all time, noted and in 1582 wrote a detailed treatise upon the vital problem of his day—syphilis and its association with aneurysm.



Vesalius about 1557 diagnosed both thoracic (and for the first time) abdominal aneurysms



Fernel first recognized internal aneurysms and suspected their relationship to syphilis as early as 1542 Later, Lancisi (1728) emphasized this relationship and published a treatise on both aortic and cardiac aneurysms

left. At the apex, there was a pronounced diastolic thrill, the first heart sound was loud and booming and was followed by a blowing systolic murmur transmitted upward and to the left. The second sound was clear and snapping and was followed by a loud, low-pitched rumbling diastolic murmur. Over the base of the heart, there was a loud to-and-fro murmur, the latter being the diastolic which was best heard in the second interspace to the right of the sternum. The

systolic murmur at this area was loud, rough, and of a lower pitch than the diastolic murmur. The first sound was completely replaced by the systolic murmur which was transmitted to the vessels of the neck The radial pulses were full and of the Corrigan type There was a distinct capillary pulse and pistol-shot sounds were heard over both femoral arteries. The liver was enlarged,



FIGURE 1 Extensive syphilitic aortitis showing a marked "treebark" appearance of the aorta; thickening with deformity of the commissures of the aortic valves producing aortic insufficiency. Localized small areas of aortic dilatation

extending 5 cm. below the costal border. There was a scar on the shaft of the penis The VDRL was positive His course was rapidly downhill and he died three days after admission to the hospital

An autopsy was performed sixteen hours after death. The heart was considerably enlarged, dilated, and very flabby. The tricuspid, mitral, and pulmonic valves were normal. The posterior leaflet of the aortic valve presented a perforation, measuring approximately 0 8 cm in diameter It was thickened and firm. The edges of the fenestration were friable and slightly injected At the attachment of the valve, there was a small nodule which was swollen, hard, and firm. Examination of the aorta just posterior to the leaflet showed a distinct swelling and tendency toward corrugation. Sections made through this area showed extensive involvement of the aorta from the intima through the media to the adventitia. The intima was thick, swollen, and contained numerous round cells and fibroblasts The media was heavily scarred with fibrous tissue, numerous small round cells and plasma cells, showing their greatest collection about the blood vessels. In the adventitia, there were numerous fibroblasts, lymphocytes

and plasma cells, indicating a rather acute fulminating process, probably syphilitic. The interesting facts are that this patient received his primary infection with a positive dark-field examination, seven months prior to admission to the hospital. He developed an acute aortic syphilis which involved only a small area in the aorta and also the posterior leaflet of the aortic valve, causing gummatous degeneration of the valve with perforation and death.

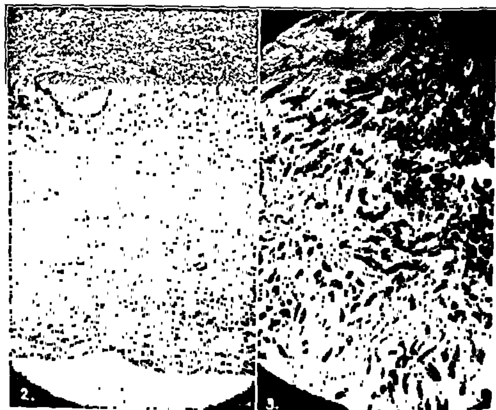


FIGURE 2 Low magnification of a section through the aorta showing infiltration of the adventitia with small round cells, destruction of the elastic fibers of the media, thickening of the walls of the vasa vasorum, marked thickening and infiltration of the intima with small round cells.

FIGURE 3 Higher magnification of degenerative changes occurring in the media

Prevalence and Distribution: In the present day it is gratifying to see the incidence of this disease decreasing due largely to the efforts of private physicians and the Public Health Service who, in addition to widely disseminating knowledge of syphilis, have also established an acceptable method of treatment of the disease, with adequate penicillin therapy. Since 1949, the rate per 100,000 population has dropped from 197.3 to 87.5 in 1954; which, in the light of past experience, is a most noteworthy achievement. Statistical data vary considerably as to the prevalence of the early involvement of those who have had syphilis. Warthin[17] from postmortem experience is of the opinion that ninety per cent of those with syphilis showed definite aortitis. Langer,[9] from the Virchow Krankenhaus, found among 23,105 autopsies on syphilitic persons from seventy to eighty

per cent with cardiovascular involvement. It is true that many of these lesions were minimal and could have been detected only at autopsy. White,[21] in 1933, found 2.8 per cent of syphilitic aortitis in 2100 autopsies at the Massachusetts General Hospital. Cowan[7] and Faulds in 1929 report six per cent in 100 autopsies at Glasgow.



FIGURE 4 Teleoroentgenogram of the heart showing marked saccular aneurysm of the aorta. The heart is normal in size

The clinical recognition of syphilitic aortitis has not kept pace with the incidence discovered at autopsy despite the fact of a greater increase in the efficiency of diagnosis. This, however, is easily explained; when a large amount of autopsy material is studied, it is readily seen that it is an impossibility to detect from physical or other examination the minimal lesions of this infection. Cochems[4] and Kemp found among 1000 individuals

with syphilis, 12.7 per cent who had cardiovascular syphilis. Turner among 6000 patients was able to recognize 10.1 per cent with cardiovascular involvement. In 15,000 autopsies at the Philadelphia General Hospital, Welty[19] found cardiovascular syphilis in 6.93 per cent. Maher,[21] Sittler, and Elliott discovered syphilitic heart disease in 9.7 per cent of 1000 patients seen in private practice. In the cooperative[6] clinical studies among a group with late syphilis, there was an incidence of ten per cent in 6263 patients. Congenital syphilis can produce cardiovascular degenerative changes affecting chiefly the myocardium, as was shown by numerous case reports. These cases are of more academic than clinical interest since very few so infected survive for any length of time.

Age and Race: Cardiovascular syphilis is much more frequent in the South than in other parts of the United States, largely because of the Negro population. The factor of age in acquired cardiovascular syphilis is of some importance, as the manifestations usually occur from ten to twenty years after the primary lesion. This places the greatest age incidence between thirty and fifty years, which is between the age groups of patients with rheumatic heart disease on the one hand and the group of those with arteriosclerotic or hypertensive heart disease on the other.

The majority of cases are found in the fourth decade, with the fifth and third following closely. There are, of course, cases occurring in much younger and much older individuals In the Negro race, either because of the lack of inherent racial immunity, or due to acquiring the disease earlier in life, we find cardiovascular involvement occurring at a much younger period.

Among the Whites, as well as among the Negroes, there will be approximately four males to one female. This discrepancy is usually explained by the fact that men perform much more arduous work than women, causing a more severe strain on the aorta. However, one must not lose sight of the fact that the promiscuity of the male is much more than that of the female, which makes him decidedly more liable to contract the disease.

Social status is definitely related to the occurrence of syphilitic infection. It is well known that the uneducated and ignorant races are much more prone to have the infection than people of higher intelligence. It is of importance to recall that among the ignorant there is frequently no treatment for this infection, and adequate treatment is very rare. Time and close observation alone will tell the effect which intensive penicillin therapy will have on the percentage of involvement of the cardiovascular system in syphilis.

Pathology: Involvement of the aorta is almost the universal lesion in latent syphilis. The pathological picture of syphilitic aortitis is quite characteristc and very seldom mistaken for any other lesion It is one of marked cellular infiltration, involving as a rule all three layers of the aorta; and along with this there is hyaline destruction of tissue with evidence of healing and replacement by fibrous tissue and formation of new blood vessels with resulting scarification.

There are many different ideas advanced by various authorities as to the mode of infection. Some think the Treponema is carried directly to the

aorta from the primary lesion and there sets up a chronic inflammatory lesion. In support of their claims they cite the frequent findings of the Treponema in the aorta of patients who have died from other causes, during early syphilitic infection.

Klotz[25] advanced the idea, with considerable evidence to support his view, that the Treponema passed to the aorta through the lymphatics of the mediastinum after having been trapped in the mediastinal lymph nodes, where they produce a mediastinitis. Saphir and Scott[13] and Backhaus are of the opinion that the end result, which is medial degeneration, is due to an endarteritis of the vasa vasorum produced by a proliferation of the cellular elements within these small blood vessels, which interferes with the nutrition of the media.

Gross examination of the aorta reveals well-outlined, elevated, gray, translucent patches which may be discrete or may coalesce to form larger areas. These streaks or patches run lengthwise of the aorta and usually begin just above or at the aortic sinuses and proceed upward to the arch, involving it and occasionally the abdominal aorta, although in most cases of syphilitic aortitis the process usually stops where the aorta passes through the diaphragm. This is not always true, for occasionally the abdominal aorta alone may be the only part involved. Very rarely do these typical lesions degenerate and form ulcers. The latter condition is more commonly found in atheromatous degeneration, which may also be associated with syphilitic aortitis.

If the inflammatory process involves the aorta around the ostia of the coronary arteries, as it frequently does, serious difficulties may arise It is of interest that the ostia of the coronary arteries may show extensive disease, yet very rarely will the disease progress further into the arteries themselves. The microscopical picture is very characteristic. In the adventitia and about the vasa vasorum in the media, one finds a collection of small, round, singly nucleated cells with plasma cells and fibroblasts. The infiltration, beginning in the adventitia, proceeds into the media, where the blood vessels gradually become narrowed and almost completely obliterated. The round cells, the plasma cells, and the fibroblasts so infiltrate the connective tissue and the elastic tissue that hyaline degenerative changes are most marked. One can frequently see strands of elastic tissue that are broken and widely separated from each other, and between these fibers there is evidenced an attempt at healing by replacement with connective tissue The cells of the intima increase in number and frequently form distinct ridges which project in the lumen of the aorta.

In the media, there occurs very frequently, areas of necrosis with complete destruction of all formed elements. These areas resemble small gummata. As this destructive process continues, the vessel wall becomes weakened; and depending on the extent, there may develop either a small or a large aneurysm. Sometimes the media is completely replaced by fibrous tissue. Should the destructive change proceed downward and involve the commissures of the aortic valve, or should it involve the valve itself, we find marked retraction, scarification and shortening of the aortic cusps or dilatation of the aortic ring, resulting in aortic insufficiency. If the infection

is extensive, and progresses more or less simultaneously, there is generalized thinning of the entire thoracic aorta, resulting in a general dilatation of the blood vessel, and a resultant aneurysmal dilatation. The commonest complication of syphilitic aortitis is aortic insufficiency which is present in approximately fifty per cent of the patients who have been correctly diagnosed. Very rarely is it seen early in the disease.

With thickening of the intima, a narrowing or partial obstruction of the branches of the aorta may occur. This has been mentioned as occurring at the ostia of the coronary arteries; the innominate, the subclavian, the intercostal, and the carotid arteries may likewise be involved.

Symptoms: A striking feature of syphilitic aortitis is its latency. As a rule, there are no symptoms early in the disease, and even later, there may be no manifestations. The early diagnosis of cardiovascular syphilis resolves itself, therefore, into the early recognition of latent infection of the aorta, which would seldom be necessary if every patient with primary syphilis received early and adequate treatment. When it is possible to make a clinical diagnosis of aortitis, we have seen from the discussion of the pathology of the disease that much irreparable damage has been done.

Symptoms, generally speaking, result from involvement of the aorta in one of three ways: (1) The aortic valve or its commissures becomes diseased, resulting in incompetency, which leads to cardiac hypertrophy, dilatation, and finally congestive failure; (2) dilatation of the aorta, either diffuse or saccular, with or without symptoms, due to pressure on adjacent organs; (3) involvement of the ostia of the coronary arteries, resulting in myocardial ischemia. The two outstanding symptoms for which the majority of patients seek relief are substernal oppression and pain, or paroxysmal attacks of dyspnea.

In the early cases pain is not severe, and is usually noticed only after strenuous exertion. It seldom radiates and is localized beneath the upper part of the sternum; it is not an agonizing pain, but more a pressure or burning sensation which lasts for a short time and which, as soon as there is a period of rest, completely disappears. The pain frequently is associated with mild dyspnea or a slight, nonproductive cough. In an otherwise healthy individual who has been free from substernal discomfort, the onset of pain, in the absence of hypertension, with a positive VDRL, should make one suspicious of luetic aortic involvement. When the ostia of the coronary arteries are involved, there may occur the typical symptoms of coronary insufficiency.

Physical Signs: Because of the latency of the manifestations of cardiovascular syphilis, there may be no physical signs whatsoever, and only too frequently is the evidence discovered at postmortem examination. On the other hand, with involvement of the aorta, one may occasionally find rather obvious signs of the disease. These physical signs are those of arotic dilatation, which were described so clearly and distinctly by McCrae[23] in 1910. These consist very briefly in: (1) An increase in the percussed area of dulness over the upper part of the sternum. The heart in practically every uncomplicated case of syphilitic aortitis is normal in size and there is no hypertension. (2) In a number of cases, there may be seen pulsation

in the first and second interspaces to the right of the sternum or in the suprasternal notch; with this there may be observed a slight thrusting forward of the upper part of the sternum. (3) Over the aortic area, one frequently hears a soft, systolic murmur which is transmitted to the vessels of the neck. (4) Of greatest importance is the loud, amphoric, tambour-like aortic second sound heard best to the right of the sternum in the second interspace. When obtained, this is an extremely characteristic and valuable sign, perhaps the most valuable, and differs in quality from that heard in patients with hypertension. It is generally stated that this is present in practically all patients with aortic insufficiency.

Additional information may be obtained by a fluoroscopic examination of the heart and aorta. An experienced observer can easily detect widening of the aorta with an increase of aortic pulsation. In a patient with an aneurysm, the roentgen ray furnishes the deciding evidence in the diagnosis, and by its employment one can frequently detect not only one but several saccular dilatations.

The electrocardiogram gives very little additional aid in making a diagnosis. Smith[15] and Blackford studied tracings made from 128 patients with *syphilitic aortic incompetency and in comparing these with 900 tracings* made from patients with other types of heart disease, found that the following changes occurred with significantly greater frequency in the syphilitic group: (a) Intraventricular conduction defects; (b) left axis deviation; (c) low voltage T wave; (d) S-T segment deviation. Arrhythmia was rare. Transient auricular fibrillation occurred in only 3.1 per cent of the syphilitic group.

Blood tests are of considerable value in establishing the presence or absence of syphilis. One must realize, however, that these tests are positive in approximately only eighty per cent of patients with syphilitic aortitis and that if the blood reaction is negative, one should not entirely dismiss the diagnosis of syphilitic aortitis.

Complications: It is unfortunately too true that a great number of patients with cardiovascular syphilis are undiagnosed until some of the three complications arise The diagnosis then is quite evident but the patient has reached that stage of the disease when all chances of a cure have gone and when all one can hope for is to salvage as much as possible from the wreckage, by prolonging life with adequate treatment directed toward the care of the patient, his heart, and his syphilis.

AORTIC INSUFFICIENCY

This is the commonest complication observed and occurs with a variable degree of frequency in different hospitals, depending greatly on the clientele During a four year period, among 224 patients with cardiovascular syphilis admitted to the Emory University Division of Grady Hospital, 142 or sixty-three per cent had aortic incompetency.

Pure *aortic insufficiency occurring between the ages of thirty and sixty* years among Whites, and at an earlier age in Negroes, in the absence of a history of rheumatic fever, arteriosclerosis, or hypertension, is practically always due to syphilis.

ANEURYSM

This is the next most frequent complication of cardiovascular syphilis. To understand the significance of this complication, one must bear in mind that an aneurysmal dilatation may occur at any place in the aorta and be of any size. On the medical service of the Emory University Division of Grady Hospital, there is practically no place in the aorta where we have not seen an aneurysm, and these have varied in size from 1 to 2 cm., to 15 to 20 cm. in diameter. They occur most frequently in the ascending portion of the aorta and the aortic arch. Next in frequency is the descending and abdominal aorta. Aneurysms are accompanied in about ten per cent of cases with aortic insufficiency. Depending on their size and location, they may be with or without symptoms and are frequently discovered only at postmortem examination.

Among our group of 224 patients with cardiovascular syphilis, there were 54, or twenty-four per cent, with aneurysms.

ANEURYSM OF THE ASCENDING AORTA

These are usually small and occur intrapericardially. The aneurysms originate most frequently in the aortic sinuses but may occur in any portion of the aorta. There are usually no associated symptoms or physical signs unless the aneurysm ruptures with a resulting hemopericardium or increases sufficiently in size to compress surrounding structures such as the pulmonary artery. On rare occasions these aneurysms may become so large that the heart is displaced downward and to the left.

The following case history illustrates the devastating effect of the rupture of a small aneurysm producing sudden death in an otherwise healthy active colored male.

This forty-one year old waiter was admitted to the hospital in obvious shock and complaining of pain in his chest. He had always been well with the exception of six injections in his arm for "bad blood" several years previously. On the morning of admission he had noted a vague pain in the upper part of his right chest He ate a hearty breakfast and reported for work at 1:00 o'clock At 2:00 o'clock he developed a sudden intense pain in the midline of his chest just beneath the manubrium, radiating downward toward the abdomen and finally becoming very intense in the lower anterior chest and upper abdomen.

Physical examination revealed a normally nourished male in profound shock with an unobtainable blood pressure, cyanosis, distant heart sounds, feeble but equal peripheral pulses, and right upper abdominal tenderness and rigidity. Urinalysis revealed a three-plus albumen. The leukocyte count was normal The Wassermann reaction was strongly positive.

Morphine and local measures were of no benefit and the patient died twelve hours after the onset of pain.

Autopsy revealed a diffusely dilated ascending aorta and aortic arch. Two centimeters above the beginning of the aorta there was a bulging of the aorta one centimeter in diameter and depth. At the tip of this small aneurysm there was a small perforation from which a large quantity of blood had escaped into the pericardial sac. There was some thickening about the coronary ostia. The aortic valves were competent. The aorta showed a diffuse syphilitic aortitis for a distance of five centimeters from its beginning to a short distance beyond the left subclavian artery.

The following record illustrates the effect of an aneurysm originating in the region of the aortic sinuses which increased sufficiently in size to almost completely occlude the pulmonary artery.

A thirty-two year old colored male laborer was admitted to the hospital with the complaints of "short breath, pain around the heart, weakness, and swelling." He had always been in good health. Two years prior to admission he noted an exertional non-disabling palpitation For two months prior to admission there had been a progressive development of dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. For three weeks the patient had chest pain with burning primarily in the left chest and generalized edema.

Physical examination revealed a normally developed edematous male in great respiratory distress. Respirations were thirty to the minute and the blood pressure in both arms was 140/20. There was a striking generalized edema, dilatation of the neck veins, and visible carotid pulsations. Numerous fine rales were audible over both lung bases The entire precordium was thrust forward with each systole. The point of maximum impulse was in the sixth interspace twelve centimeters from the midline The percussed area of dulness was increased to the right, five centimeters from the midline in the fourth right interspace A systolic thrill could be felt over the apex and pulmonic area. On auscultation at the apex there was a very loud systolic murmur which increased in intensity and was loudest over the pulmonic area. A diastolic murmur was heard best over the aortic area, but both murmurs were easily heard over the entire precordium The pulses were regular and equal, of the Corrigan type The Wassermann reaction was positive. The patient died the second day after admission. At autopsy there was an aneurysm originating near the aortic sinuses pressing against the pulmonary artery almost completely occluding it Syphilitic aortitis and involvement of the aortic valve was also noted.

ANEURYSM OF THE AORTIC ARCH

It is difficult clinically to separate aneurysmal dilatations of the aortic arch into those involving the various portions of the arch. Only occasionally are these dilatations localized in one section.

Symptoms and Physical Signs: These depend on the point of origin of the aneurysm, the size, and the structures that are compressed or destroyed by the aneurysmal growth and movement. A large number of aneurysms cause no symptoms.

Pain: *This is the commonest complaint and varies in intensity, severity,* and location. In the beginning it is a mild but more or less constant discomfort which is not increased by exercise or excitement but may be aggravated by change of position. It frequently is referred to the anterior chest wall, the neck, the back, and occasionally the arm. It usually does not come in paroxysms, but is described as neuralgic in type. This "neuralgic type" pain is frequently followed later in the course of the disease by a constant, boring type pain that is usually associated with destruction of bone. The milder type pain is related to pressure on nerve roots or other structures adjacent to the aorta.

Cough: This is usually nonproductive and frequently only an irritative hack. As pressure on the trachea or bronchus increases, the cough usually increases in severity. Hemoptysis occurs with sufficient irritation or rup-

ture of the aneurysm. There is very frequently a so-called "goose cough" associated with paralysis of the left vocal cord.

Shortness of Breath: This is usually the result of displacement of the lung in the thoracic cage by the tumor mass or due to pressure on the trachea or bronchi.

Hoarseness: This is due to enlargement of the aortic arch and the resulting paralysis of the left recurrent laryngeal nerve.

Dysphagia: This is not a common symptom and is due to pressure of the aneurysm on the esophagus.

Physical Signs. *Inspection:* Engorgement of the veins of the neck, arms, or chest due to pressure of the tumor on the superior vena cava is sometimes found At times the tumor erodes the ribs or the sternum and may be seen as a large pulsating mass extending five or six centimeters above the chest wall and covered only by the tightly stretched glistening skin.

Palpation: Deviation of the trachea from the midline and demonstration of the tracheal tug is of great importance. There is occasionally noted a difference in the radial pulses and a marked difference in the blood pressure in the arms. The expansile quality of the pulsation is best determined by placing one hand over the suspected area and the other hand at an opposite point on the back. This sign varies with the thickness of the clot that fills the aneurysmal sac. A systolic thrill is frequently palpable over the pulsating mass.

Percussion: The heart is of normal size unless the aneurysm is associated with aortic incompetence. There is increased retromanubrial dulness and occasionally increased dulness to the right of the sternum. In aneurysms of the descending aorta there is a definite impairment of the percussion note on the left posteriorly if the tumor mass is near the spine.

Auscultation: This procedure is of little value. A systolic murmur can be heard over the tumor if the clot is not too thick. It should be remembered that the pressure of the aneurysm will occasionally produce the signs of aortic incompetency without involvement of the valve.

A rather typical patient was admitted to the hospital complaining of pain in the left chest and shortness of breath. He was perfectly well until one year previously when an upper respiratory infection left him with hoarseness and pain in his upper left chest, shoulder, and back. Six months before admission he was awakened with very severe pain in the interscapular region In the following six months this pain increased and became more constant and was accompanied by a cough productive of blood-tinged sputum The patient had untreated syphilis six years previously.

Physical examination revealed an orthopneic male. The left pupil was larger than the right; both reacted. There was a distinct tracheal tug and paralysis of the vocal cord. Respiratory movements were limited on the left. The upper left chest was flat on percussion, and breath sounds and whispered voice were inaudible. There was a visible and expansile pulsation over the manubrium with marked increase in retromanubrial dulness to percussion. At the apex there was a soft systolic murmur followed by a loud rumbling diastolic murmur heard less distinctly at the base.

The patient remained in the hospital for one month and died suddenly after a paroxysm of coughing productive of a large amount of blood

At autopsy the whole upper mediastinum was filled with a large aneurysmal sac extending to the left and backward, eroding the first and second thoracic vertebrae, pressing on the trachea, and completely obstructing the left bronchus Rupture of the aneurysm occurred into the left bronchus. Microscopic examination showed the pathological picture of syphilitic aortitis.

ANEURYSM OF THE ABDOMINAL AORTA

This is the rarest type of aortic aneurysm. It usually occurs near the celiac axis and the symptoms, when they occur, are produced by pressure on spinal nerves, erosion of the vertebrae, or pressure on neighboring structures. Diagnosis is oftentimes difficult unless a pulsating mass can be felt. In recent years aortograms have been of great value diagnostically.

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MORTIMER S. FALK, M.D.
AND
JOHN H. STOKES, M.D.

10

Treatment of Cardiovascular Syphilis

Historical Note: Syphilis had been recognized as a cause of cardiovascular disease in the sixteenth century, but it was not accorded due prominence as an important etiologic factor in affections of the heart and blood vessels until the second half of the nineteenth century. As was to be expected, the most obvious form of cardiovascular syphilis, *i. e.*, aortic aneurysm, was the first to attract attention.

Although aneurysm of the external arteries was described in antiquity by Galen, it was Andreas Vesalius[1] (1514-1564) who in the sixteenth century first recognized aneurysm of the aorta without mentioning, however, its association with syphilis. Ambroise Paré[2] (1510-1590), one of the contemporaries of Vesalius, first suggested this relationship, but appeared uncertain whether the syphilis itself or the accompanying mercurial cachexia was the responsible factor. The distinguished Roman physician, Giovanni Mario Lancisi[3] (1654-1720), was convinced by his anatomic studies that syphilis played the etiologic role and referred to venereal aneurysms ("aneurysma gallicum") in his superb monograph published posthumously.

Among the writers of the eighteenth century, Morgagni made numerous and important contributions to the literature of the subject, but for the next three quarters of a century nothing was added, and the earlier teachings seemed practically forgotten. The modern views on cardiovascular syphilis date from the latter half of the nineteenth century with the appearance of the studies of Helmsteder,[4] Welch,[5] Heiberg,[6] Malmsten,[7] and Dohle,[8] and others from Heller's pathologic institute in Kiel. The importance of syphilis as a cause of cardiovascular disease is now well established. Although in very recent years there appears to have been a decrease in its incidence, it still accounts for a significant percentage of deaths due to cardiovascular diseases in adults.

Fundamental Principles: The fact that syphilis of the heart and great vessels is thought of less as syphilis than as heart disease is the source of many blunders in treatment In evaluating the patient with late syphilis, it must be remembered that the disease attacks many systems, either singularly or concurrently. It is necessary, therefore, at the outset to recall certain fundamental principles of the treatment of syphilis as a disease which govern the treatment of syphilis as appiled to its lesions in the cardiovascular system. First, let it be recalled that syphilis contributes un-

favorably to practically all pathologic processes and, accordingly, treatment for syphilis is indicated in cardiovascular disease whether the syphilis seems causative or merely coincidental. The weight of this dictum in cardiac disease is gradually achieving recognition. It should be remembered even in the management of the decompensated heart where rest, sedatives, digitalis, and diuretic measures are prescribed, but antisyphilitic treatment may be omitted. The possible failure of such general measures to restore a heart until appropriate treatment for the syphilitic infection has been instituted is demonstrable.[9]

The second therapeutic consideration in treating cardiovascular syphilis is that of *therapeutic shock* (Jarisch-Herxheimer reaction). In the arsenical and heavy metal era of syphilis therapy it was held that fast-acting treatment such as is afforded by the arsphenamines and bismuth, especially in large doses, could cause focal flare-ups of the syphilitic process. If such flare-ups with accompanying edema occur in a partially occluded cononary artery, the wall of an artery weakened by aneurysm, or an infiltrated myocardium or conduction mechanism, the gravest results may follow the first or even the first several treatments with these drugs. Accordingly, it was generally accepted as axiomatic that flare-up at active foci in the affected tissues in syphilitic cardiovascular disease should be carefully prevented by a choice of slower-acting nonshock-producing drugs as preparation for any more intensive subsequent treatment, and by a reduced dosage, whatever the preparation used.

In the last decade penicillin, and to a much lesser extent the other antibiotics, have replaced the arsenicals and heavy metals as the treatment of choice for all stages of active syphilis. Penicillin is as potently spirocheticidal as the arsphenamines, if not more so, and produces Herxheimer reactions, even in relatively small dosage, in fifty to seventy-five per cent of patients with early syphilis.[10,11] Paradoxically, reports on penicillin in cardiovascular syphilis have minimized the dangers of therapeutic shock.[12,13,14,15] This holds true for patients in congestive failure.[16,17] While isolated case reports of severe untoward reactions,[18] interpreted to be possible instances of therapeutic shock, have appeared in the literature, those papers which summarize experiences with relatively large groups of cardiovascular syphilis patients have, almost without exception, emphasized the tolerance demonstrated to this form of treatment. When one considers the widespread and at times indiscriminate use of penicillin in recent years for relatively minor ailments, it becomes apparent that many undiagnosed cases of previously untreated cardiovascular syphilis have received the antibiotic without experiencing severe reactions of therapeutic shock.

The now extensive experience with penicillin indicates that it is the safest of all potent spirillicidal agents which have been used in the treatment of cardiovascular syphilis. Nevertheless, it should be pointed out that there are investigators who still state that "preparation"* with bismuth and iodides[19,20] or mercuric cyanide[21] should precede penicillin therapy. We must temper our advocation of penicillin only slightly by em-

* There is some evidence that preparation with less potent spirillicidal agents will not prevent the occurrence of the Jarisch-Herxheimer reaction [14]

phasizing careful work-up of all patients and hesitancy where there is evidence that therapeutic shock might be severe. This is applicable principally in patients who have evidence of coronary ostial involvement.

The third consideration concerns the induction of so-called *therapeutic paradox*.[22] By this term is meant the exaggeration of symptoms and the unfavorable outcome which may follow the rapid and fibrotic type of healing induced especially by the arsphenamines. It was held as a fact that rapid symptomatic response in syphilitic cardiovascular disease could be postively dangerous, and that a patient who was up and about, or who had returned to work in six weeks, might be unnecessarily dead in six months as a result of his therapeutic miracle. This entire concept is now controversial. If it does occur, it is extremely rare following penicillin therapy.[12,23,24]

A fourth group of considerations in the treatment of cardiovascular syphilis is the preventive aspect. In the arsenical and heavy metal era inadequate treatment of early syphilis was the rule rather than the exception and progression to late symptomatic cardiovascular syphilis such as aortic insufficiency or aneurysm was inevitable in a relatively high proportion of patients. Penicillin has changed this. We now have an agent which is apparently capable in the majority of cases of eradicating every focus of *Treponema pallidum* in a relatively short treatment period. From the aspect of preventive medicine this has already reduced the incidence of cardiovascular syphilis. However, it must be remembered that relatively small amounts of penicillin such as are used to treat gonorrhea, respiratory infections, and many other infections are capable of masking early symptoms of syphilis without curing the disease. This widespread practice could leave a reservoir of undiagnosed "latent" syphilis which will later manifest symptoms of tertiary syphilis such as cardiovascular involvement. This is pointed out because it is one of the reasons why routine serologic tests for syphilis premaritally and as part of hospital admission studies and complete physical examinations should be encouraged.

The importance of early diagnosis and treatment of syphilis cannot be overemphasized. Barring this, a high index of suspicion in persons presenting the earliest suggestive indications of aortic disease will uncover cases at a period when comparatively greater myocardial reserve and better condition of the coronary vessels provide an opportunity for arresting syphilitic cardiovascular disease before irreparable damage has occurred. With present day diagnostic measures such as the treponema immobilizing antibody test, cases which were formerly equivocal or borderline can now be diagnosed with more certainty.

In line with the principle of therapeutic paradox, there may be noted in the response of a syphilitic aortic lesion the so-called paradoxical exaggeration of signs with improvement of the patient's condition. For example, a diastolic murmur and transient slight dilatation with edema and dyspnea, followed by hypertrophy and restoration of compensation, may result from the initiation of treatment in a patient who, at the outset, presented only a systolic murmur in the aortic distribution. This paradoxical healing effect is not to be interpreted as a treatment failure, but probably as a treatment success.

The Appraisal: The first step, to precede all treatment for syphilis of the cardiovascular system, must be an appraisal of the patient's condition and resources—mental, physical, material. The weak spots in the treatment of cardiovascular syphilis are the myocardium and the coronaries. In appraising the myocardial situation, electrocardiographic studies are essential in addition to the experienced appraisal of the functional capacity of the heart muscle. There is no such thing as a distinctive syphilitic electrocardiogram, but there is important information to be gained as to the status of the syphilitic patient's heart from this examination. It was believed that patients with inverted T waves in Lead I, and with markedly aberrant Q-R-S complexes, could be hastened to their deaths by the arsphenamines. It was accepted good practice that slower acting drugs be given by nonintensive methods in such cases. Experience with penicillin has, in the main, tended to minimize the dangers of this powerful spirocheticidal agent in patients with marked electrocardiographic changes.[25]

The myocardial reserve of the syphilitic cardiovascular patient must be carefully appraised. Arteriosclerotic changes in general, hypertension, and the cardiorenal status must be considered important influencing factors in the prognosis. Age, while not infallible, may be a helpful guide in the consideration of treatment approaches. The patient who finally in his fifties goes to the wall with a decompensated syphilitic heart has very little recuperative power. Much less can be expected of him in the way of treatment response than of the younger patient whose aortic murmur and evidence of syphilis is discovered while his heart muscle is perhaps still far from exhaustion.

The not uncommon coincident occurrence of neurosyphilis and cardiovascular syphilis as well as occasional visceral lesions such as gummata or syphilitic hepatitis indicates that a complete pretreatment evaluation of each patient is essential. This should include a cerebrospinal fluid study in almost all cases and visceral "function" tests when indicated. Without baseline pretreatment studies, the patient's posttreatment progress is difficult to evaluate.

Therapeutic Agents: Previous editions of this text included a discussion of the more commonly used chemotherapeutic agents such as arsphenamine, neoarsphenamine, the arsenoxides, bismuth arsphenamine sulfate, (Bismarsen [R]), the mercurial salts, the bismuth salts, and the iodides, Since most of these are no longer advocated in the treatment of syphilis, this discussion will be limited to penicillin with brief mention of bismuth, the iodides and mercury for those who choose to "prepare" the occasional patient who might seem to be a candidate for severe therapeutic shock.

Consider first penicillin. There is little doubt that this spirocheticidal antibiotic is a useful therapeutic tool. It has a distinct advantage over old forms of chemotherapy in that its toxicity in low. However, an increasing number of allergic reactions ranging from various degrees of urticaria to anaphylactic shock (sometimes fatal) and periarteritis nodosa have been occurring. The literature on penicillin in cardiovascular syphilis has, with few exceptions, emphasized principally the paucity of reactions of the therapeutic shock and therapeutic paradox type. On the positive side,

direct persumptive evidence of penicillin's effect is presented in Sinclaire and Webster's interesting histologic study of autopsy material from a small (ten) group of patients with aortitis, aneurysm, or aortic insufficiency.[26] They observed that the syphilitic inflammation (lymphocytic and plasma cell infiltration) was almost or completely absent in patients who had received penicillin more than ten weeks before death but marked in those who had been treated more recently.

Optimum time and dosage schedules for penicillin, if they can be determined, are still unknown. The observations which have been reported have included wide variations in total dosage and length of treatment time. The largest series are based on patients treated with five to twelve million units given in divided doses over periods ranging from ten days to three weeks. Earlier reports indicated the use of crystalline penicillin G in aqueous solution given in doses approximating 40,000 to 80,000 units every 2 to 3 hours around the clock. More recently, results with procaine penicillin G (300,000 to 600,000 daily) have been published. The tendency has been toward an increasing dosage. Breutsch concluded from histopathologic studies of the aorta, that the syphilitic inflammation is resistant to treatment and the total dosage of penicillin should, therefore, be 25 million units divided into daily doses of 400,000 to 600,000 units.[27] While such large amounts may be unnecessary, for the present it is best to err on the side of overdosage.

The broad spectrum antibiotics (chlortetracycline, oxytetracycline, and chloramphenicol) are known to have pronounced antispirochetal activity. They have not yet been sufficiently evaluated to advocate their routine use in cardiovascular syphilis. However, it might be well to keep these antibiotics in mind for possible use when the patient with severe allergic penicillin sensitivity requires treatment. There is no basis for advocating a specific dosage schedule but using favorable results observed in neurosyphilis as a precedent, one could give two to four grams daily to a total of sixty grams.

For the most part, the chemotherapeutic agents have become syphilotherapeutic history. We shall allude to a few briefly for those who fear penicillin in a difficult situation where severe therapeutic shock might have been expected in the arsenical era. Mercury, it was believed, practically never produce significant therapeutic shock effects, for its actions on the disease are slow and indirect, probably by allowing the host's cellular defense mechanism to cope with the infection. The soluble salts such as mercuric succinimide, or mercuric cyanide given intramuscularly in dosage of 0.01 Gm. daily are used. Considering its negligible antispirochetal effect and its relatively high toxicity, there would appear to be very little justification for the use of mercury.

Bismuth is more rapid in action and more shock-producing than mercury and less so than the arsenicals. Most cardiovascular patients will undoubtedly tolerate it in full therapeutic dosage from the start. Insoluble bismuth salts such as bismuth subsalicylate are given intramuscularly at four to seven day intervals in doses of 0.1 to 0.2 Gm.

Neither bismuth nor mercury should be given intravenously to patients with cardiovascular disease. The toxic dose is too near the therapeutically effective dose by this route, and the need for time saving can be met satisfactorily by the use of a soluble salt intramuscularly.

The iodides, although still used on occasion in all forms of cardiovascular syphilis, are also for the most part therapeutic history. Doses of 0.3 to 2 Gm. of sodium or potassium iodide, three times a day, may be employed alone or, more commonly, along with the heavy metals. The digestive disturbance, coryza, and rash are rarely disturbing factors if the drug is given just before meals in water, not milk, in a concentration of 240 cc. (8 ounces) of water to each 3.3 Gm. (50 grains) or less; and if the larger doses are begun from the outset and not reached by way of a minute initial dose and subsequent 0.064 Gm. (1 grain) accretions The writers have seen no clinical evidence of increased toxicity of potassium as compared with sodium iodide in syphilitic cardiovascular disease.

General Treatment Measures: It is, of course, as important to emphasize to the practitioner and the syphilologist that the syphilitic with a heart complication must be managed as a heart case as to remind the cardiologist and internist that the syphilitic cardiovascular patient has syphilis The digitalization and the management of decompensation of the syphilitic heart should be supervised by one familiar with the general principles. Rest should not only be employed in the advanced case, but it should also be made available, or activity should at least be curtailed, in the patient with aortitis with valvular involvement while the adjustments in heart load, due to shrinkage of healing valves, are taking place.

The great importance of integrity of the aortic valve in the future of the patient is very apparent in comparing the behavior under treatment of aneurysm and aortic regurgitation. To secure rest for the syphilitic heart is sometimes rendered difficult by the wreckage of the patient's morale on the familial, social, and stigmatic aspects of his condition. *Time spent, therefore, in adjusting the patient's viewpoint may be as important as drug therapy.* Occupational therapy and progressive relaxation are very helpful. There are no incompatibilities between the sedatives usually employed and any form of antisyphilitic medication. The tonic effect of penicillin sometimes encourages undesirable gains in weight that must be watched.

Relief of pain in patients with repeated anginal seizures sometimes becomes a critical matter, and the use of various methods of nerve block and resection upon the cervical sympathetic are sometimes justified for the control of this particular phase of the problem. There is no more inveterate relapser than the once-decompensated aortic regurgitant patient, and preventive measures should be taken, if possible, before rather than after the first breach of compensation has developed. It cannot be overemphasized that it is extremely important to avoid decompensation by every means, *i. e.,* restriction of activity at the outset even to the point of strict bed rest if necessary and permanent adjustments of the future mode of life of the patient. The importance of this is reemphasized by data of the Cooperative Clinical Group[28] which show that of 281

patients with syphilitic aortic regurgitation or aneurysm, forty-two cent of those in whom congestive heart failure was present before tr ment died, and their average duration of life was thirty months; o twenty-four per cent of those in whom heart failure was absent bef treatment died, and their average life duration was forty-seven mon In water-logged cases, the diuretic effect of mercuhydrin, mercupu salyrgan, neohydrin, and the cation-exchange resins should be kept mind.

Special Considerations. ***Aortitis, Aortic Regurgitation and Ao Aneurysm:*** In the arsenical-heavy metal era it was held that the keyn for successful treatment of the various manifestations of cardiovascu syphilis lay in the clinicians' ability to individualize the type and tensity of therapy to suit the needs of each patient. Preparatory tre ment with iodides and bismuth or mercury were recommended even *uncomplicated aortitis* because of the possibility of severe or even fa *therapeutic shock effect of arsenicals on clinically undetectable coron* artery involvement. In patients with aneurysm or aortic regurgitati *the approach was often even more conservative. It was held that if su cient cardiac reserve could not be established by the preparatory tre ment, it might not be possible to use an arsenical at all, except perh in the form of small doses of bismuth arsphenamine* sulfonate (B marsen®). In retrospect, it must be remembered that the dangers pro bly lay not only in the possibility of producing severe therapeutic sho but also in the vasculotoxic properties of the arsenicals.

Today, although every consideration must be given to the cardiac a general physical status of the patient, one can generalize about penici dosage in all forms and stages of syphilitic cardiovascular disease. Exc in an equivocal situation where coronary ostial involvement or extrem thin walled aneurysm is known to exist, penicillin may be started in dosage from the start. Many will argue that even these exceptions do n exist. Penicillin is given as the prolonged action procaine-penicillin *dosage of 600,000* units daily to a total of ten to fifteen million or m *units.*

Reversal of the Serologic Tests for Syphilis: The blood serologic t for syphilis should not be used as a gauge of arrest or progression cardiovascular syphilis. While it is desirable to reverse the blood serolo test for syphilis, especially in the earlier cases, it is not justifiable overtreat the patient in the effort to secure an often unattainable ne tive serologic test for syphilis.

Surgical Procedures for the Treatment of Aneurysm: Recent impro ments and innovations in cardiovascular surgery have included techn for reducing or eliminating vascular aneurysms. Wiring of well-defin aneurysms of the aorta and larger vessels is a palliative procedure wh *may afford the patient considerable relief from pain and provide prot tion from imminent rupture.*[29] A "pack" *method of intrasaccular wir* in which 100 to 500 *feet of stainless* steel wire is inserted in aneurys of the aortic arch will result in thrombosis and often prevent furt dilatation.[30] In suitable cases, excision of aneurysms and restoration

continuity by means of aortic hemografts have been successfully performed. When possible, this may be the procedure of choice.[31]

Syphilitic Myocarditis: Recent studies have demonstrated clear-cut electrocardiographic evidence of myocardial invasion in approximately fifty per cent of patients with primary and secondary syphilis. The great majority of these respond completely to routine penicillin therapy.[32]

Peripheral Vascular Disease Accompanying Syphilis: It is out of the ordinary to see peripheral vascular disease in patients with syphilis exhibit more than equivocal therapeutic results. It is true, however, that hypertension in the syphilitic patient sometimes undergoes marked and apparently lasting reductions under treatment. Since the nature of essential hypertension is so much in dispute, and apparently so rarely syphilitic, the source of these good effects must remain in question. In general, it may be said that the hypertensive patients tolerate treatment with penicillin quite well.

Endarteritic processes with gangrene and examples of thromboangiitis obliterans, accompanied by positive blood serologic tests for syphilis, do not furnish a very satisfying field for syphilotherapy. Almost any form of treatment may produce a transient improvement, perhaps nonspecific in origin, only to be followed by relapse and progression on which further treatment for syphilis has little or no influence. There are, however, no actual contraindications to an intelligently directed therapeutic test if the serologic test for syphilis is positive.

Effects of Treatment: A valid statistical appraisal of the value of antisyphilitic treatment in the various stages and degrees of cardiovascular syphilis has always been extremely difficult. There are so many variables including among others, the problem of making the diagnosis of uncomplicated syphilitic aortitis, the difficulty of defining adequate treatment in the prepenicillin era, the compilation of reliable data on a significant number of untreated or very little treated control series of patients, the coincidence of other forms of tertiary syphilis such as neurosyphilis, and the lack of patient cooperation for prolonged periods of observation, that available statistics are subject to criticism on these and other bases It is hoped that more reliable information on the effect of penicillin in this form of syphilis may be compiled in the future.

The Cooperatve Clinical Group's statistical survey[28] of cardiovascular syphilis comparing treated *vs.* nontreated patients is quoted from, primarily because it is based on a large series (619 patients):

In uncomplicated syphilitic aortitis the average duration of life was increased from thirty-four to eighty-five months in patients who had received thirteen or more injections of an arsenical plus interim heavy metal after the diagnosis was made; sixty-three per cent of patients who received adequate treatment were living and symptom-free with no progression of the cardiovascular condition at the time of study as compared to forty-nine per cent of those who received inadequate treatment.

In patients with syphilitic aortic regurgitation, the average duration of life was increased from forty to fifty-five months with adequate treatment after diagnosis was made; symptomatic relief was obtained in sixty

per cent of patients who received adequate treatment. In the group with saccular aneurysm, the average duration of life after detection of the aneurysm was thirty-seven months in patients who had inadequate treatment, and this was increased to seventy-five months in patients who received adequate treatment.

Barnett and Small in a careful statistical analysis[33] of 334 patients with syphilitic aortic regurgitation or saccular aneurysm concluded that the effectiveness of specific treatment definitely declines as the disease advances. They also found that the mortality was seventeen per cent higher in their poorly treated patients than in a comparable group who received "much" treatment.

Preventive Aspects: The treatment of cardiovascular syphilis, like that of neurosyphilis, is undertaken years too late. Unfortunately, the diagnosis of early cardiovascular syphilis is not easy to make, and many cases go unrecognized until they have progressed to the stage of aortic regurgitation or aneurysm. One aid to the prevention of serious cardiovascular syphilis is recognition of early uncomplicated syphilitic aortitis by maintaining a high index of suspicion and critically evaluating each patient by means of diagnostic criteria, such as outlined by Moore, Danglade, and Reisinger.[34] There is no certainty that modern treatment pushed to its utmost can prevent the progress of the disease, even at this early stage, for examples of progression were seen in the prepenicillin era in spite of treatment.

The hope is cherished that identification of a syphilitic infection in the early or even the latent stage, and its treatment with an adequate course of penicillin, will protect the patient from syphilitic cardiovascular disease. It is now within the province of the practicing physician, who sees the patient when he presents himself with a chancre or secondary eruption, to prevent the relatively discouraging situation with respect to cardiovascular syphilis from ever arising. That adequate treatment of the patient with early syphilis is, in fact, a protection in later life is shown by the fact that in the Cooperative Clinical Group material[25] of 333 patients who received adequate and regular treatment during the early stages, and who were followed for from three to twenty years, not one developed any of the graver forms of cardiovascular syphilis By the intelligent use of penicillin during the early infectious stages, and adequate posttreatment follow-up examinations of the patient, the practitioner may attack cardiovascular syphilis at its root. The rational approach to cardiovascular syphilis today is the intensive and thorough-going treatment of primary and secondary syphilis.

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DAVID P. BARR, M.D.

II

The Heart in Diseases of the Endocrine Glands

DISEASES OF THE PITUITARY GLAND

Pituitary Insufficiency (Simmonds' Disease, Pituitary Dwarfism)

Destruction, removal, or functional insufficiency of the pituitary gland is followed by generalized atrophy of all organs and especially of the thyroid, suprarenals, and sex glands. While the heart participates in this wasting process, clinical evidence of cardiac weakness is not usually apparent. Blood pressure may be low, normal, or high. Tendency to hypotension is in general less than in primary adrenal insufficiency.[1,2] Patients with pituitary insufficiency are, however, subject to attacks of extreme weakness and low blood pressure. This is attributable to inadequate function of the adrenals, resembles the crisis of Addison's disease, and may be corrected by administration of sodium chloride and adrenal hormone. Such attacks may be precipitated by unwise attempts to correct too rapidly the concomitant hypothyroidism by administration of thyroid.

Acromegaly and Gigantism

Eosinophile tumors of the anterior lobe of the hypophysis are usually if not always responsible for the development of the clinical syndrome of acromegaly and preadolescent pituitary gigantism. They produce somatic changes, with general overgrowth of all structures most obvious in bones but affecting practically all tissues. The heart may be enormously enlarged. While this is perhaps chiefly attributable to the participation of the heart in a generalized hypertrophy, there are many cases in which the enlargement is out of proportion to that observed in other structures. One contributory factor may be hyperthyroidism, which has been noted in approximately 50 per cent of acromegalics. Diabetes, a frequent concomitant, may predispose to coronary disease. Changes in the vascular system may be evident early. Blood pressure is variable, in some cases being as low as 100 or less, while in others it has exceeded 200 mm. Hg.

Size of some acromegalic hearts is impressive. Zondek[3] observed radiograms of the heart with transverse diameters from 15 to 17.6 cm. In Lewis' patient,[4] a man 1.88 meters (6 feet 2 inches) in height weighing 113.4 kg. (250 pounds), the heart weighed 620 Gm. Kraus[5] studied a man 1.78 meters (5 feet 10 inches) in height whose heart weighed 950 Gm.

The largest heart in an acromegalic weighed 1295 Gm. and was reported by Humphry and Dixon.[6] Most remarkable of all reported cases was a man studied by Osborne[7] over a period of approximately six years. At the time of his death he was forty-eight years of age. His height was 1.75 meters (5 feet 9 inches), and it was estimated that he weighed approximately 136.08 kg. (300 pounds). He died of syncope in a manner described by Marie as typical of death in acromegaly. The heart was enormous. It weighed 1163 Gm. (2 pounds 9 ounces) and measured 0.38 meters (15 inches) in its greatest circumference. The wall of the right ventricle was 9 mm. (3/8 inch) in thickness, while that of the left ventricle measured 21 mm. (7/8 inch). Valves were normal except for slight thickening at the edges of the aortic cusps. The wall of the aorta was not diseased. The coronaries, although nowhere occluded, were so enlarged as to admit an ordinary lead pencil to their mouths. It could not be stated with certainty whether hyperthyroidism had contributed to the enormous cardiac hypertrophy. The thyroid gland, however, was enlarged, and there was in the upper mediastinum an accessory thyroid which was thought to be hyperplastic. That the enlargement of the heart was not due entirely to secondary factors such as hyperthyroidism is indicated by the fact that the weight of the liver and of the kidneys was more than twice the average normal.

Heart failure is not infrequent in acromegaly. It was noted in eighteen of twenty-four cases collected by Mason;[8] six of his patients died from this cause. In twenty-one cases reviewed by Hejtmancik and his associates,[9] thirteen had clinical evidence of heart disease, five were frankly decompensated, two had episodes of left ventricular failure; nine of fifteen had abnormal electrocardiographic tracings, and impaired intraventricular conduction was found in six. Literature concerning the heart in acromegaly has been reviewed by Houssay and Houssay.[10]

In the early stages of preadolescent pituitary gigantism, there may be extraordinary strength and vigor. Later, most giants become pitifully weak, with edema of the extremities and other evidences of circulatory insufficiency.[11,12] The exact status of these cases has been inadequately analyzed. The enlargement of the heart bears a normal relationship to body size.[13] When one considers the enormous food requirement of some of the larger giants it seems not unlikely that vitamin B deficiency may at times contribute to circulatory failure.

Pituitary Basophilism (Cushing's Syndrome)

Cushing[14] was responsible for the discovery that tumors of the basophile cells of the pituitary gland are not infrequently accompanied by symptoms which include obesity of face, neck and trunk, hirsutism, wasting of muscles, decalcification of bones, polycythemia, hypertension, impotence in men, amenorrhea in women, and not infrequently glycosuria or even frank diabetes. Later studies have shown that while in these cases the pituitary gland is usually structurally abnormal the syndrome is chiefly attributable to disease of the adrenal cortex with disturbance to be regarded as secondary in pituitary, hypothalamus, thymus, and gonads. Circulatory disturb-

ances referable to Cushing's syndrome will be discussed under the section devoted to diseases of the suprarenal glands.

DISEASES OF THE PARATHYROID GLANDS

General Considerations: Diseases of the parathyroid glands present problems of great interest because of accompanying variation in calcium content of serum and because of the known physiologic effect of calcium concentration upon contractility of cardiac muscle.

Under normal conditions calcium is maintained in serum with constancy at a concentration of approximately 10.0 to 11.0 mg per 100 ml. In hypoparathyroidism following the removal or destruction of the gland the serum calcium may be reduced to a level as low as 4.0 mg per 100 ml., the reduction being chiefly if not entirely in the fraction which may be considered physiologically active. On the other hand, in hyperparathyroidism which accompanies hyperplasia or adenomas of the gland, the calcium level has been recorded as high as 29.4 mg. per 100 ml. of serum. Again this extraordinary increase cannot be ascribed to a greater concentration of protein or of other factors binding calcium in an inactive form, but must be attributed to an increase in the physiologically active fraction.

The effect of varying calcium concentrations upon cardiac function has been extensively studied. In perfusion experiments it has been found that the presence of calcium in the circulating medium is necessary for the contraction of cardiac muscle. A frog's heart perfused with sodium chloride solution soon ceases to beat, but can be restored by the addition of calcium and potassium to the perfusion fluid. On the other hand, calcium salts themselves are toxic when their concentration is unduly increased or when they are not properly counterbalanced by sodium and potassium. Within certain ranges the isolated heart of the frog is extremely sensitive to relatively small changes in calcium content of the nutrient fluid. Indeed the response is so delicate that the frog heart preparation has been used as a means of estimating physiological variations in the ionized calcium of serum and other body fluids.[15] In the perfused rabbit heart it has been shown that slight variations in the calcium concentration of the perfused fluid produce notable changes in the force and duration of systole

Hypoparathyroidism

From these experimental observations it might be anticipated that the heart would be notably affected by the reduction in serum calcium which accompanies hypoparathyroid tetany. Actually the clinical manifestations of functional cardiac changes have not been obtrusive. During the frequently long course of the disease, pulse, blood pressure, and circulation are usually maintained at essentially normal levels. The electrocardiogram, however, has revealed changes which are worthy of note and which are in general similar to those which have been observed in experimental animals.[16,17] Particularly notable has been the prolongation of systole,[18] which in some cases may be extreme. Skouge's[19] case, a patient with thyrotoxicosis, had a Q-T interval of 0.37 before thyroidectomy. Tetany developed immediately after the operation and was persistent. There was

a progressive prolongation of the Q-T interval, which three months after the onset of tetany was 0.62 seconds. Marzahn[20,21] observed a patient with postoperative tetany in whom the systole was prolonged to 0.48 seconds. Restoration of normal serum calcium by means of dihydrotachysterol resulted in systoles of normal duration.[22]

During severer attacks of tetany the circulatory changes may be considered a consequence of muscular exertion and do not differ materially from those observed in other spasmodic or convulsive states. In children, however, sudden death has rarely occurred during sustained paroxysm and has been attributed to spasm of the cardiac muscle.

Hyperparathyroidism

Shortly after the introduction of parathormone its effect on the heart and circulation was thoroughly studied by Edwards and Page.[23] To dogs they administered from twenty to fifty Collip units at intervals of two to four hours. The total amount injected varied between thirteen and forty units per kg. of body weight and resulted in an elevation of serum calcium from normal to values between 15 and 22 mg. per 100 ml. During the early stages of the experiment the heart rate was increased slightly. Later there was slowing and usually a marked arrhythmia with premature beats and shifting of the pacemaker function. There were, however, no constant changes in the electrocardiogram. In some records the P waves underwent progressive increase in height during the period of treatment. Direct observations on the heart displayed dilatation of the right auricle and it was thought that the change in P waves might have resulted from a greater activity of a slightly stretched auricle. There were also changes in the amplitude and direction of the T waves. The changes in cardiac function following overdosage with parathyroid extract were compared with those found after injection of large amounts of calcium salts with the conclusion that the effects produced were similar, if not identical.

In clinical hyperparathyroidism there are usually no signs or symptoms of heart disease. Hypercalcemia manifests itself in the electrocardiogram by a shortening of the Q-T interval and a consequent shortening of ventricular systole, although the length may still be within normal limits.

Many cases of hyperparathyroidism are complicated by bilateral nephrolithiasis, which may eventually lead to pyelonephritis, hypertension, and circulatory insufficiency.[16,17]

HYPOTHYROIDISM (MYXEDEMA HEART)

Active interest in the heart in myxedema started with the report of Zondek in 1918.[24] In a study of four advanced cases he demonstrated that both the right and left chambers of the heart might be greatly dilated, that the cardiac action was slow and indolent with normal blood pressure, and that the electrocardiograph revealed characteristic and striking changes. He showed further that these evidences of cardiac involvement could be modified or even reversed by effective treatment with thyroid. To designate this clinical condition he introduced the term "myxedema heart."

Zondek's observations were repeatedly confirmed[25,26,27] and led to clinical and experimental studies which established the significant effects of prolonged hypothyroidism upon the heart and circulation.

Pathology: At autopsy some degree of dilatation or hypertrophy of the heart has usually been demonstrable. Of the twenty autopsied cases collected by the Clinical Society of London,[28] one-third revealed thickening of the muscle of the left side of the heart. In nine autopsies studied by Means[29] a pseudohypertrophy possibly due to swelling of muscle fibers was grossly evident in several. It has been suggested by many observers that the changes in the heart may be attributed to an edematous condition of the cardiac muscle similar to that seen in other tissues of myxedematous patients. Microscopically, however, a variety of pathological changes has been described.[30] Among these are destruction of muscle fibers, thickening of the leaflets of the aortic valve and accumulations of a homogeneous material which has an affinity for hematoxylin but which does not display the staining characteristics of the myxedematous infiltration found in the skin.[31]

In thyroidectomized animals, hearts have been shown to be dilated, pale and flabby. *Microscopically there has been a decrease in the number* of muscle fibers with degeneration and disappearance of perinuclear sarcoplasm in some of those which remain [32] Simpson[33] found that early thyroidectomy in sheep presented abnormal development of the sarcoplasm. Edema has been shown not only by the gross appearance of the muscle itself but also by measurements of actual water content.[34]

Our knowledge of the exact pathologic change in the heart in myxedema and of the true nature of Zondek's so-called myxedema heart has been greatly handicapped by paucity of autopsy examinations of completely untreated subjects. Brewer[34a] recently reported an autopsy of a man of middle age who had never received treatment for an advanced myxedema There was some fluid in the pericardium. The left ventricle was moderately enlarged. Patchy atherosclerosis was seen in the coronary arteries and throughout the course of the aorta and its main branches. Microscopically there was some fibrosis as well as amorphous basophilic infiltration of muscle fibers.

Effusion into the pericardium has been found both in autopsied cases of myxedema and in experimental hypothyroidism.[32,34,35] This may be accompanied by ascites and by pleural effusion. Means[29] states that in his experience the serous cavities of untreated cases invariably contained fluid. In one of the autopsied cases of the Massachusetts General Hospital there were 3000 cc. of serous fluid in the peritoneal cavity, 1500 cc in the two pleural spaces, and 1000 cc in the pericardial sac.

The question has often been asked whether Zondek's diffusely enlarged heart that attained normal size so readily after thyroid therapy might in reality represent massive pericardial effusion. The cases in which this hypothesis has been tested have not been numerous

Kern and his associates[35a] in 1949 were able to collect twenty-one cases in which great enlargement of the heart shadow had been noted and myxedema heart of Zondek had been suspected. In all the subjects, peri-

cardial tap revealed massive effusion. Kern himself was able to demonstrate pericardial effusion in four consecutive patients having myxedema even when roentgenologic findings were not suggestive of the presence of cardiac enlargement and in the absence of any signs of congestive failure. He and his associates expressed the belief that pericardial effusion is an early and constant factor in myxedema and a major factor in the explanation of the so-called myxedema heart. They think also that the electrocardiographic changes formerly explained as due to myocardial weakness can better be attributed to a blanketing effect of the fluid in the pericardial sac.

Lesions of the arteries have been frequently demonstrated. Atheroma was apparent in more than half of the twenty autopsied cases of the Clinical Society of London,[28] although in only rare instances was the condition advanced. Sclerosis of aorta, coronaries, and other arteries was shown in the early studies of von Eiselberg.[36] Pick and Pineles[37] found similar changes following thyroidectomy in young goats. The idea that hypothyroidism should contribute to premature and extensive arteriosclerosis derives support from the hypercholesterolemia, which is a frequent accompaniment, and from an apparently greater incidence of angina pectoris. Autopsy examinations on untreated cases have been insufficient to establish such a relationship. Blumgart and his associates[38] reported their experiences with patients seen at intervals after therapeutic thyroidectomies or other measures intended to produce complete hypothyroidism; they were not impressed that the tendency to atherosclerosis had been exaggerated. In five patients surviving from three to eleven years in the hypothyroid state careful studies revealed minimal or no coronary atheroma.

As early as 1908 Saltykow[39] suggested that the arterial lesion of myxedema resembled medial necrosis. This idea has received support from the demonstrations by Kountz and Hemplemann[40] of spontaneous aortic rupture in three cases in which complete thyroidectomy had been performed during the course of malignant hypertension. Examination revealed aortic lesions apparently identical to the cystic medial necrosis of Erdheim.[41] Exactly similar lesions have been noted in a severely myxedematous patient who had during life no evidence of hypertension.[42]

Clinical Manifestations. *Functional Disturbances:* In the myxedematous state, it has been shown that the velocity of blood flow is diminished and that the cardiac output per minute and per beat is decreased. Studies of arteriovenous oxygen differences have revealed that the circulation rate is less than could be accounted for by the lower oxygen requirements of the tissues.

Enlargement of the Heart: The size of the heart shadow in the teleoroentgenogram is increased in most myxedematous patients. Of forty-eight cases studied by Lerman, Clark and Means,[44,45] thirty-four showed a transverse diameter of the heart which exceeded by 1 cm. or more, one-half the diameter of the chest; in twenty-two the transverse measurement was 5 cm. or more in excess of half the chest diameter.

The cause of the enlargement is still a subject of dispute. That it is

not due to hypertrophy of the cardiac musculature is clearly indicated by the rapidity with which the size of the heart decreases during treatment The most obvious explanation would be that the heart, like other tissues, contains an increased amount of interstitial fluid. Pathologically, however, the extent of demonstrable edema of cardiac muscle does not readily account for the clinical observations. Dilatation of some degree has usually been assumed and has been demonstrated in many autopsied cases and in the hearts of thyroidectomized animals.[26] Gordon[40] has suggested that the supposed enlargement of the heart is attributable to accumulation of fluid in the pericardium. He emphasized that the appearance of the roentgenographic shadow of the myxedema heart of Zondek closely resembles that of pericardial effusion; also, that fluoroscopically the heart borders move sluggishly in both conditions. Fahr has stressed as possibly the only point in differential diagnosis that the diameter at the base of the heart is much narrower in myxedema than it is in the presence of massive pericardial effusion. Unfortunately, in some cases[46] of myxedema with excessive accumulation of fluid in the pericardium this differentiating sign has been absent. In considering the available evidence certain facts must be emphasized: (1) That pericardial fluid has been demonstrated clinically in a number of cases of advanced hypothyroidism;[46,47,48,49] (2) that some degree of accumulation of fluid in the pericardium of autopsied cases has been an extremely common finding; and (3) that in most of the clinical cases of gross enlargement of the heart in myxedema the possibility of pericardial fluid has not been entirely excluded.

Clinical evidence indicates that great enlargement of the cardiac shadow is encountered only after a patient has been in a hypothyroid state for several years. The degree of physical activity and of other factors of strain such as hypertension are no doubt contributory. Zondek's[50] German officer was shot through the thyroid gland in 1914. Three years elapsed after the destruction of the gland before severe signs of cardiac involvement developed. Fahr[51] observed a patient who had been successfully treated for myxedema but who had discontinued therapy. Eight months were required before an enlargement of 3 cm. in the transverse diameter of the heart could be demonstrated.

Cardiac Decompensation: In the literature there is no agreement as to the incidence of congestive heart failure. Of 162 cases of myxedema studied by Willius and Haines,[52] 91 per cent were said to be free of subjective or objective signs of organic cardiovascular disease. In the remaining 9 per cent the lesions were accounted for by etiological factors other than myxedema. On the other hand, Fahr,[45] in a study of seventeen cases, found five with evidence of serious heart failure, while eight others showed dyspnea, pitting edema, reduction in vital capacity, rales at the pulmonary bases and some degree of dilatation of the heart. It is difficult indeed to explain such varied experience. Most observers agree that extreme degrees of decompensation are uncommon, except when other organic heart disease is present as a complication. White[53] states that he has never seen congestive failure as a cause of death in myxedema.

Angina Pectoris: The association of precordial pain with myxedema was noted as early as 1914 by Hertoghe[54] and was mentioned by Zondek[50] in his original account of the myxedema heart in 1918. Characteristic angina pectoris was reported by Laubry[55] in 1924. Although complaint of precordial aching is not uncommon the incidence of severe pain appears to be quite rare. Willius and Haines[52] in their 162 cases of high grade myxedema mention only one in whom twinges of pain followed the full use of thyroid. Lerman, Means and Clark[44] saw one case of angina in eighteen patients, while others[56,57,58] make no mention of the symptom.

Hypertension: Zondek in his original description of the myxedema heart specifically mentions the normal blood pressure accompanying the cardiac enlargement. Actually hypertension is by no means rare. Among ninety cases studied by Froment and Jeune,[59] twenty-two showed pressures above normal, fifty-nine were within normal limits and only nine revealed hypotension. In Means'[29] forty-eight patients the blood pressure before treatment varied from 88/64 to 190/130. In the fatal case of Lenegre and Fleurot[60] the blood pressure was 220/110. Thompson and his coworkers[61] have presented evidence that the incidence of hypertension is greater in successfully treated myxedematous patients than it is in the general population.

Cardiac Irregularities: Sluggish heart action with slow pulse is apparent in most well-advanced cases of hypothyroidism. In some patients with low metabolism, however, the heart rate may be accelerated. Auricular fibrillation is rare[62,63,64] Gardner[65] in a single case noted periods of auricular flutter with arborization block. Nodal paroxysmal tachycardia alternating with sinus bradycardia was reported by Lisser and Anderson[66] Paroxysmal auricular tachycardia has also been noted.[62] Increased auricular-ventricular conduction time is not very uncommon.[62,67] A high degree of partial heart block was reported by Luten.[68]

Electrocardiographic Changes: Some degree of abnormality in the electrocardiogram is extremely common in myxedema and in cretinism. Froment and Jeune[59] found pathological changes in 106 of 163 cases, Ohler and Abramson[62] in thirteen of twenty-one cases, while Lerman, Clark, and Means[43] found abnormalities in all of their patients with well-developed myxedema. The most constant feature is a flattening or inversion of the T waves, particularly in Lead II. This may be accompanied by abnormal axis deviation, by a diminution in the amplitude of the QRS complexes and by small P waves. Such changes are observed in many cases of hypothyroidism in which thorough clinical and radiographic examination reveals no cardiac abnormality. The exact cause of the electrocardiographic changes is not clear. The suggestion that they might be due to the altered resistance of myxedematous skin has not been substantiated. That they are not attributable directly to the decreased rate of oxidation is shown by the work of Reid and Kenway,[69] who found no abnormalities in the electrocardiograms of persons having low metabolism without myxedema.

Treatment: If a patient has not been too long neglected and if there are no serious complicating arterial lesions, treatment may be extremely

satisfactory. Digitalis has been notably unsuccessful in relieving failure of myxedematous hearts. Thyroid, on the other hand, accomplishes in most cases prompt and often dramatic improvement.

Following thyroid medication the sounds of the heart gradually become more audible and the pulse rate increases. As the basal metabolism returns to normal, the output of the heart per beat and per minute is increased and the *velocity of blood flow is augmented.*[43]

The size of the heart shadow diminishes. The degree of change varies but may be very great. In one of Fahr's cases there was a shrinkage of 6.3 cm. in the transverse diameter over a period of seven weeks. Ten of Lerman's[44] twelve patients exhibited progressive decrease in cardiac measurements, reaching a maximum in periods varying from three weeks to six months.

Diminution in the abnormalities of the electrocardiogram is apparent in almost all treated cases and may develop rapidly. Flat or inverted T waves become normal in appearance, the amplitude of the QRS complex is increased and the P waves become normal or in some cases unusually prominent.

The effect of thyroid medication on the level of blood pressure cannot be predicted. Changes were noted in thirty-seven of Means'[29] forty-eight cases. In twenty of them the systolic pressure dropped 10 mm. or more, while in eleven cases it rose 10 mm. or more. Variable changes were also noted in the level of diastolic pressure. In most of the patients there was slight increase in pulse pressure. A gratifying result of treatment has been noted in some of the cases in which hypertension has been a feature.[70] In Means' series, fourteen patients had high blood pressure before the institution of therapy. In five of these, the blood pressure returned to normal, while in six others the level of blood pressure was lowered.

Thyroid therapy has at times affected the rare cardiac irregularities of myxedema. In two[62,64] of three cases of auricular fibrillation, the use of thyroid without other drugs was followed by a return to normal sinus rhythm. Gardner's[64] auricular flutter with arborization block, the nodal tachycardia of Lisser and Anderson,[66] and the paroxysmal auricular tachycardia of Ohler and Abramson[62] disappeared following thyroid medication.

It should be emphasized that there is usually no compelling reason for rapid administration of thyroid in cases of myxedema. Changes consequent to the hypothyroidism have progressed over a period of months or years. Rapid return to a normal state may be accompanied by discomfort, and in patients who present evidence of cardiac decompensation or signs of arteriosclerosis of the coronaries or other vessels, may be extremely hazardous.

In the rare case of cardiac failure thyroid medication by increasing the metabolism and thereby increasing the work of the heart may precipitate an *acute decompensation. A more imminent danger presents* itself in *patients whose coronary vessels are extensively diseased.* In 1925 Christian[71] reported a case of a woman of fifty years who died of coronary infarction sixteen days after thyroid medication was begun. Since that

time a number of accidents have been reported.[72,73] These have been recently collected by Smyth.[74] It is notable that the accidents have occurred in patients past middle life with ages running from forty-nine to sixty-three. In these cases the coronary attacks have occurred under circumstances which suggest a causal relationship rather than mere coincidence.

In the treatment of most cases of myxedema and especially of those discovered in later life or exhibiting signs of cardiac involvement or arteriosclerosis, the initial dose of thyroid should not be greater than 0.06 Gm. (1 grain) per day. Correction of hypothyroidism results in increased oxidative rate and greater work of the heart. The possible deleterious effect of this change should be minimized by restriction of the patient's activity during the early period of treatment. This may be cautiously increased as the tolerance and requirements of the patient become apparent. When myxedema is accompanied by cardiac disease, the patient should be resting and under constant and detailed observation. If during the period of readjustment there is any evidence of cardiac difficulty, the medication should be withdrawn for several days and then resumed in smaller dosage.

DISEASES OF THE SUPRARENAL GLANDS

Addison's Disease

A small heart and a small aorta have frequently been described in Addison's disease and have been regarded as due to an atrophy secondary to the hypotension and the inactivity enforced by the persistent weakness and debility caused by the disease. The condition of the heart was carefully studied by Barker,[75] who was able to assemble twenty-one cases in which the heart had been weighed. Using the table of average normal weight with upper and lower limits, as devised by Smith from total body weights, Barker found that the weight of the heart was less than the average normal in fifteen cases, and greater than the average in six. This would seem to indicate that there is actually a specific diminution in the size of the heart as an accompaniment of Addison's disease. The deduction, however, is rendered somewhat invalid by the fact that most patients with Addison's disease, particularly those in whom there is an accompanying tuberculosis, tend to lose large amounts of weight and that a certain amount of atrophy of the heart may be expected from loss of weight due to any cause.

Significant abnormalities in the electrocardiogram were encountered in 60 per cent of Thorn's[76] sixty-four cases and in approximately half of these, were suggestive of myocardial disease. The fact that over 50 per cent of the abnormalities appeared in patients under the age of forty and that twenty of thirty-five were seen in women indicates a specific effect of adrenal insufficiency upon the heart muscle. In one of our cases of addisonian crisis acute but reversible changes characteristic of myocardial infarction were encountered. In Thorn's series no electrocardiographic pattern could be regarded as specific for Addison's disease. The changes were extremely variable, including prolonged PR and QT intervals, low QRS voltage and low or inverted T waves. Other less frequent changes included absence of

the initial upward QRS deflection in the chest lead, small initial upward QRS deflection in the chest lead, sinus bradycardia with a cardiac rate of less than fifty per minute, premature ventricular contractions, and ST segment depression of less than 1 mm.

In spite of their small hearts, their electrocardiographic abnormalities, and the dyspnea and palpitation they experience after slight exertion, untreated patients with Addison's disease seldom, if ever, develop cardiac decompensation. Since the introduction of adrenal hormones, however, and particularly after excessive doses of desoxycorticosterone acetate or cortisone, myocardial failure has been frequently encountered. The circulatory weakness of the chronic adrenal insufficiency may have been a significant factor in its development.

Optimal hormonal treatment restores normal blood pressure and normal plasma concentrations of sodium chloride and nonprotein nitrogen. Excessive doses may cause sudden increases in blood volume and blood pressure *as well as abnormally high sodium and chloride contents of serum and* interstitial fluids. It may result in cardiac dilatation, pulmonary edema, peripheral edema, or even sudden death. McGavack[77] has suggested measurement of heart size as a means of checking whether optimal dosage of hormone has been exceeded.

Other than mechanical factors may contribute to the circulatory difficulty. Excessive doses of adrenal hormone may be followed by abnormally low concentrations of potassium, at times so extreme as to lead to transient peripheral motor paralysis. The hypokalemia itself may result in widespread myocardial fibrosis with areas of focal necrosis in heart muscle Similar changes have been seen following potassium-deficient diets[77a,77b] and after injection of desoxycorticosterone acetate[77c] and have been demonstrated clinically in the case reported by Goodof and MacBryde.[77d]

Serious cardiac decompensation may result and may be accompanied by electrocardiographic changes which perhaps in part reflect variations in the concentration of potassium.[78] Treatment with the hormone is successful in correcting the electrocardiographic changes of Addison's disease in only a few cases Seven of forty-one patients in Thorn's series showed significant improvement in the electrocardiogram during therapy, while fourteen exhibited an increase in the number and extent of the abnormalities. Changes attributable to the therapy include low voltage of QRS waves, prolongation of the PR interval, prolongation of the QT interval, and T wave inversion which may resemble that of myocardial damage or coronary insufficiency.

Aldosterone in Congestive Heart Failure

It is *now known that the adrenal cortex is responsible for the production* of an antidiuretic hormone which may play an important role in producing edema of cardiac decompensation.[78a] The mechanism by which production of this hormone is stimulated during heart failure is complex and as yet not completely understood. Level of aldosterone in the blood during early decompensation is not high but as the heart failure develops the mechanism for its production is gradually established. With increasing

venous blood volume and pressure there is a gradual simultaneous diminution in effective cardiac output with decreased volume and pressure or blood flow in all or in portions of the arterial circulation. This stimulates reflexly through a hypothalamic center the production of aldosterone-stimulating hormone, which in turn stimulates the adrenal cortex to produce the antidiuretic hormone, aldosterone.

In circulatory failure the kidney is already handicapped in its elimination of water by a decreasing glomerular filtration rate. This factor may be, however, of less importance in the production of edema than aldosterone, which augments reabsorption of sodium by the renal tubules.

Cortical Tumors and Hyperplasia of the Suprarenals

Increased function of the suprarenal cortex appears now to be essential to the development of Cushing's syndrome. Anatomically, hyperactivity of the gland may result from the formation of benign or malignant tumors or from a simple hyperplasia of the cortical cells. The syndrome probably results from the effect of continued excessive secretion of adrenal cortical carbohydrate-regulating hormones.[79] Stimulation of the adrenal cortex by the adrenal corticotrophic hormone of the pituitary (ACTH) may stimulate activity of the adrenal cortex, but there is general agreement that the physiologic changes encountered in Cushing's disease are the result of abnormal adrenal cortical hormone secretion and are not due to the action of ACTH as such.

Several factors in the Cushing's syndrome contribute to circulatory disturbance. Hypertension, both systolic and diastolic, is usually a prominent feature of the disease. In Raab's[80] series, high blood pressure was evident in twenty-four of twenty-six cases in which blood pressure readings were mentioned. Readings of systolic above 200 mm. Hg are frequent. In autopsied cases in which the heart has been described, hypertrophy, sometimes quite gross, has been a feature. Arteriolar sclerosis of vessels in many parts of the body may be extreme. Death has occurred from apoplexy.[81] Presence of diabetes probably contributes to the development of atherosclerosis, although comparative studies of the precocity and degree of atheromatous lesions in Cushing's disease and appropriate controls are not available. Some cases have been reported with elevated basal metabolic rates, but thyrotoxicosis is by no means a constant feature, and hypertrophy of the heart cannot usually be attributed to associated hyperthyroidism.

Another factor that may contribute to circulatory disturbance in Cushing's syndrome is disturbance in electrolyte equilibrium with tendency to accumulation of sodium and consequent overhydration increases in blood volume and added strain upon the heart. This is evident also when cortical hormones are given therapeutically in other conditions.

Chromaffin Cell Tumors

In 1922 Labbé, Tinel and Doumer[82] reported a case of a married woman of twenty-eight years who suffered from frequent paroxysmal attacks of high blood pressure, during one of which she developed a fatal pulmonary

edema. Autopsy revealed a tumor of the left adrenal gland. Five years later C. H. Mayo[93] successfully removed an adrenal tumor from a young woman with similar symptoms, which were completely and permanently relieved by the operation. Pincoffs[94] in 1929 reported the first case in which preoperative diagnosis was made.

Sudden and wide fluctuations in arterial pressure are not unusual in essential hypertension and have been noted in association with a number of pathologic conditions. When, however, fluctuations are marked and particularly when they are paroxysmal in character, presence of a pheochromocytoma or tumor of adult chromaffin cells of adrenal medulla or of some part of the sympathetic chain must be suspected.[85,86]

Pheochromocytoma is not so rare a tumor as was formerly thought. In 1940,[87] 103 cases could be collected, but by 1950 the number was increased to 270.[88] It has been estimated that pheochromocytoma may be responsible for 1000 deaths in the United States each year.[89] Because of its usually benign character and because its surgical removal may result in complete clinical cure, early recognition is of consummate importance.

Paroxysms may occur spontaneously or may be induced by change in position or temperature or by emotional stress, hyperventilation, physical exertion, operative procedures, massage or blows to the abdomen, or pain. In many cases systolic pressure has exceeded 300, and in one patient was recorded at 340 mm. Hg.[90] Diastolic pressure is more variable and even with excessive systolic pressure may be only moderately elevated. It has, however, been recorded as high as 240.

In the same patient paroxysms may display great variability; they may last for minutes or hours. Some milder attacks pass almost unnoticed, while others are accompanied by alarming symptoms. Palpitation due to a rapid and vigorous action of the heart is an almost constant accompaniment. Extremities usually become blanched, cold, mottled, and sometimes painful. There may be nausea and vomiting, violent headache, and drenching sweats. Pain in lumbar or other muscles may be distressing

Precordial pain with radiation to the neck and down the arm has been frequently noticed. If the attacks are severe or prolonged there may be signs of cardiac incompetence with sudden engorgement of the veins of neck, enlargement of liver, and pulmonary edema.

The electrocardiographic changes during paroxysms have been variable and are not sufficiently characteristic to aid in diagnosis. Very high T waves have been reported. In one case there were cardiac irregularities at the end of attacks with short runs of auricular tachycardia, ventricular extrasystoles, and ventricular tachycardia. Diphasic T waves have been observed in the first lead In another case a shift of the pacemaker from the sinoauricular to the auriculoventricular nodes was noted.

Between attacks there may be no symptoms. In the early stages of the disease the blood pressure is usually if not always normal. When the condition lasts long enough, however, the pressure tends to become permanently elevated. At times the permanent changes have been seen to develop rather rapidly, as in the case of Rabin,[91] in which in six months

the blood pressure between attacks had risen from 140/80 to 210/130. Electrocardiograms which have been studied between attacks in about one-half of the cases are usually normal; in others, evidence of left preponderance, notching of the T waves and large T waves have been reported.

Recognition of pheochromocytoma depends in part upon pharmacologic tests which may be classified into two groups: provocative agents that induce paroxysm of hypertension during normotensive interval, and adrenergic blocking agents that cause fall in blood pressure from its paroxysmal or sustained high level. Provocative agents have included histamine, tetraethylammonium chloride, tetraethylammonium bromide, and methacholine. Adrenergic blocking agents have included benzodioxane, Regitine (phentolamine), and dibenamine. Successful use of these tests requires many precautions, and no one of them can be as yet regarded as infallible.

A method of diagnosis from estimation of urinary catechols was introduced by Engel and von Euler.[92,93] Epinephrine and other catechol derivatives are normally excreted in urine in conjugated form. Normal daily output of the two substances amounts to only twenty to forty micrograms. In pheochromocytoma excretion may be increased ten to fifty times.

Surgery on patients with pheochromocytomas has in many instances resulted in dramatic relief of symptoms and restoration of health. It is accompanied, however, by considerable risk. Uncontrollable hypertension during operation has not infrequently caused death.[94] This can be prevented by prompt use of benzodioxane or Regitine or possibly by administration of dibenamine prior to surgery. Following removal of a tumor, administration of dilute solutions of norepinephrine, epinephrine, or Neo-synephrine may be necessary to control severe hypotension.

DISEASES OF THE PANCREAS

Diabetes Mellitus

While diabetes is not known to affect the heart directly, it predisposes to atherosclerosis, narrowing of coronary vessels, hypertension, arteriolar sclerosis, and severe nephritis[95] that may indirectly lead to severe heart disease. High blood pressure may precede by several years the onset of diabetes or in some cases develop during its course. Angina pectoris is frequent.[96,97,98] Coronary occlusion is a common complication and may occur at an early age. It was the cause of death in approximately 11 per cent of 139 cases at the Mayo Clinic.[99] In Warren's[100] series of 484 cases in which necropsy was performed 16.7 per cent of 395 over the age of forty died of coronary occlusion. Such statistics do not reveal the frequency of recent or healed infarctions, myocardial fibrosis, or other evidence of coronary artery disease. There is a significantly large proportion of females in cases in which diabetes is associated with severe coronary sclerosis. Combination of the statistics of Dry and Tessmer's[101] 130 cases and Warren's 440 cases in which sex of patients was reported indicated that severe coronary sclerosis was found in eighty males and fifty-eight females, a ratio of 1.4:1. This may be compared with sex incidence of nondiabetics over the age of forty, in which the ratio was 3.3 for women to 1 for men.

Marked atheroma of the aorta with some dilatation occurs particularly when diabetes is associated with hypertension. Occlusion of arteries of the legs also occurs with unusual frequency in cases of diabetes. At the Mayo Clinic a series of 130 necropsies on diabetic patients more than forty years of age, occlusion sufficient in degree to be symptomatic before death was present in 39 per cent. Forty or fifty-one such patients also exhibited severe sclerosis of coronary arteries.[99] Again, the proportion of females was greater than is usually found among nondiabetic patients. A ratio of nondiabetic men to women was 7.7:1,[102] while in the diabetics it was only 2.7:1.

It also appears that diabetic patients with occlusive disease of arteries of the legs have a greater incidence of gangrene and trophic ulcer than a comparable nondiabetic group. Hines[102] found 68 per cent of such lesions in diabetics as compared to 48 per cent of nondiabetics suffering from occlusive disease.

In diabetes death may occur from congestive heart failure but is more frequently due to coronary occlusion.

During diabetic acidosis and its subsequent treatment with insulin, great reduction in concentration of serum potassium has been noted. This has been accompanied by electrocardiographic changes characteristic of potassium deficiency.[103,104]

Hyperinsulinism

Benign or malignant tumors or hyperplasia of the islands of Langerhans may give rise to hypoglycemia, which may be accompanied by symptoms of weakness, profuse sweating, anxiety, faintness, syncope, or convulsions.[105,106] In this syndrome the heart does not appear to be primarily or obviously involved. Theoretically, however, a continued hypoglycemia might tend to deplete the glycogen content of the heart muscle and thus lead to cardiac weakness and circulatory collapse, particularly in patients who are already subject to serious heart disease

In electrocardiograms, Middleton and Oatway[107] found a depression of the T wave in all of the cases of insulin shock which they studied. In animals with insulin hypoglycemia, Soskin, Katz and Frisch[108] demonstrated inversion of T waves, which did not always return to normal after the injection of glucose solutions. Experimentally it has been shown that while the isolated normal heart is capable of storing glycogen during insulin administration, the diabetic heart does not store it unless the blood sugar is maintained well above the normal level.[109] Death from cardiac infarction has been reported after a rapid fall in blood sugar from the administration of insulin [110] Because of this evidence there has been some apprehension concerning the use of insulin in patients whose hearts are decompensated and particularly in those who suffer from angina pectoris or present symptoms of coronary sclerosis. Strouse and his associates[111] found that some of their patients with coronary disease experienced increasing precordial distress as the diabetic state was corrected by insulin. Joslin[95] has emphasized, however, that many diabetic patients with incompetent hearts have been benefited with the cautious use of insulin All

observers agree that *in cardiacs, great care must be exercised to avoid hypoglycemia. The diet should be regulated gradually and insulin should be given at first in very small doses.*

DISEASES OF THE THYMUS

Status Thymicolymphaticus (Lymphatism)

In 1889 Paltauf[112] introduced the concept of a lymphatic constitution characterized anatomically by prominence of the thymus gland and of the lymphoid tissue and at times by hypoplasia of the aorta; clinically by sudden death either spontaneously or from trivial causes. Since that time there has been much discussion concerning the nature of the condition and more recently concerning its existence. The undoubtedly important medicolegal aspects of the concept finally led the Medical Research Council in conjunction with the Pathological Society of Great Britain and Ireland to appoint a committee for its thorough investigation. Their studies were published in 1931 by Young and Turnbull.[113] The commission found little if any association between the weight of the thymus and the amount of lymphoid tissue in various parts of the body. They could discover no evidence of an association between arterial hypoplasia and an abnormally large thymus nor could they establish any valid relation of sudden death to the size of the thymus. They concluded that the so-called status thymicolymphaticus has no existence as a pathological entity. An interesting sidelight upon the original contention of Paltauf comes from studies of Hammar,[114] Boyd[115] and others who have shown that the thymus with malnutrition or disease tends to undergo rapid diminution in weight and that its normal size can only be ascertained in persons who die suddenly or after a short illness.

DISEASES OF THE SEX GLANDS

Atrophy, destruction or removal of the sex glands either in men or women may be followed by neurocirculatory symptoms. In female castrates and in women at the time of the menopause recurrent sensations of flushing or of suffocation, palpitation and tachycardia may result in serious incapacity.[116] There is no evidence that the heart itself is affected. Instability is typical of the menopausal syndrome and is reflected in fluctuations of blood pressure which may vary greatly from hour to hour. There has been much dispute concerning a possible etiological relation between the menopause and hypertension.[117] Maranon[118] believes that more than 50 per cent of women at the climacteric exhibit some elevation of blood pressure. Many others have noticed a high incidence of hypertension. It must be remembered, however, that the age of the normal menopause is also the age when arteriolar changes tend to become evident and that moderate or advanced hypertension is relatively frequent both in men and women during the fifth decade.

Women before the age of menopause are relatively free from cardiac complications of atherosclerosis. Statistics indicate that in people under the age of forty myocardial infarction is twenty-five times as frequent in men as in women,[119,120] although the reason for this is not known. Recent

work[121] has indicated significant differences in lipoprotein concentration and distribution in young men and women. In older men and women no sex difference can be demonstrated, and the constitution of lipids in plasma is altered from that seen in youth. In patients who have survived myocardial infarction the distribution of lipoproteins is extremely abnormal in an exaggeration of the picture found in older men and women.[122] It has been shown that this abnormal pattern of lipid concentration and distribution can be restored partially or completely to normal by the administration of estrogens.[123,124,125]

Attention has been directed to a possible effect of testosterone propionate upon peripheral circulation and upon angina pectoris.[126,127] Several reports have indicated that following its use anginal attacks have become less frequent, less severe, and of shorter duration.[128,129] The studies of Lesser[130,131] concerned forty-six patients, all of whom were said to be improved. In four cases this impression was substantiated by exercise tolerance tests. Injections of sesame oil, used as controls, were without effect. The response to testosterone propionate has been neither instantaneous nor dramatic and has become apparent only after several intramuscular injections. The mechanism by which its possibly beneficial effects might be accomplished has not been established. Larger series of cases[132,133] have permitted no conclusion concerning the benefit of the treatment.

Considerable doubt is thrown upon this observation by a study of lipid concentration and distribution following the administration of testosterone,[134] which in patients who have suffered one or more myocardial infarctions exaggerates the pathologic picture and in normal individuals produces pathologic changes that were previously not evident.

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HENRY M. THOMAS, JR., M.D.

12

The Heart in Hyperthyroidism

Introduction: Thyrotoxicosis is conspicuous because of its influence on the rate of the heart and many of its most distressing symptoms originate in that organ. Death, when it occurs, may be due to heart failure and Moebius[1] said: "*Die Basedow-Kranken leiden und sterben durch das Herz.*" For this and many other reasons the heart in hyperthyroidism deserves a most careful consideration.

It is a fact that as early as 1786 Parry[2] realized the connection between cardiac symptomatology and goiter, but, to his mind, the heart disease was the primary condition. His notes, published posthumously in 1825, include a series of eight cardiac cases in which goiter and exophthalmos were outstanding. He considered the thyroid and eye changes secondary to the heart disease itself.

Adlemann,[3] in 1829 spoke of "Kropfherz," but Graves,[4] Stokes,[5] Marsh,[6] and McDonnel,[7] four English observers, discussing separately the same group of cases between 1840 and 1855, were still convinced that the enlargement of the thyroid and the exophthalmos developed as a result of the heart trouble. Markham,[8] in 1858, reported "affection of the heart with enlarged thyroid and thymus glands and prominence of the eyes."

The Zurich surgeon, Rose,[9] wrote a long paper in 1877, pointing out the importance of considering the heart in operations on the thyroid gland. Forced respiration produced by compression of the trachea by the enlarged thyroid gland, he thought, weakened the heart and finally caused it to fail. His method of treatment was to perform a preliminary tracheotomy to relieve the heart of this particular form of burden The classical goiter heart of Rose was thus interpreted as a heart which had become enlarged and weakened purely through mechanical obstruction.

Moebius, and practically simultaneously Horsley,[10] and Kocher[11] (*vide* "struma cardiopathica") and F. Muller,[12] recognized the part played in this syndrome by the thyroid secretion, but, at the time, no adequate theory was produced to explain the circulatory changes. Many other writers mentioned cardiac decompensation in patients with large goiters and most of these observations were made in the goiter regions of Switzerland, Bavaria, and the Tyrol by such men as Wolfer,[13] Wette,[14] Thomas, Schranz,[15] and others.

Finally, in 1899, Kraus[16] brought forth his conception of the so-called neurotic or thyrotoxic heart which is now the accepted one in spite of a residue of confusion as to those cases which occur in patients with obvi-

ously nontoxic goiters. Lack of exact knowledge of the function of the thyroid gland caused him to attempt to include abnormalities of the heart seen in cases of cretinism and hypothyroidism. It is likely that authors from goiter districts have continued to confuse cases of myxedema heart with the heart in hyperthyroidism. Even as late as 1926, European writers[17] have thought of the cardiac disturbances in goiter as due to pressure on the trachea, the great vessels, or the vagus and sympathetic nerves of the neck. Interest, in America, is focused so emphatically on those thyrotoxic cases in which pressure phenomena play little or no part, that the writer proposes to omit, as irrelevant, any mechanical aspects of the enlargement of the gland, and proceed to a description of the "thyrotoxic heart."

Tachycardia: Tachycardia is the outstanding cardiac sign. With the patient at rest, the heart rate often is as rapid as 120 to the minute and not infrequently 180 to 200. The tachycardia varies according to the patient's activities, although it continues even during sleep. The degree of tachycardia parallels in most cases the severity of the disease and a fairly accurate guess as to the amount of elevation of the basal metabolic rate can be made from the resting pulse rate. It must be remembered that the resting pulse rate varies in different normal people from a rate of fifty to one of eighty beats to the minute, and this same proportionate variation may exist if hyperthyroidism develops so that the pulse rate of the first, when doubled, will be 100, while the second will rise to 160 under the influence of the same degree of thyrotoxicosis.

Murmurs: In the early stages of hyperthyroidism the tachycardia is not associated with cardiac enlargement, murmurs, or any evidence of decompensation, although extrasystolic arrhythmia does occur quite frequently. Later there is enlargement which is due to dilatation with very little hypertrophy. With the dilatation come murmurs which are usually characteristic of mitral regurgitation (apical systolic murmurs), but which may even simulate mitral stenosis* (apical presystolic murmur and thrill). The heart sounds are loud and snapping, the second sound increased, and the apex beat is forceful and abrupt. At times a systolic murmur[19] over the second and third left interspace may have a suggestive rubbing quality and be increased in intensity by pressure with the bell of the stethoscope. This type of murmur disappears after relief of thyroid toxicity. The strong possibility exists that this murmur may be related to dilatation of the pulmonary conus which frequently is seen in fluoroscopic and x-ray examinations of these patients. The systolic blood pressure is slightly raised and the diastolic pressure lowered, giving an increased pulse pressure with a bounding pulse and a visible increase in the systolic excursion of the carotid arteries. Pulsation of the liver and even of the spleen has been reported. Dilatation of the retinal veins and pulsation of the retinal arteries occasionally may be seen on ophthalmoscopic examination.

* This latter variety of murmur was shown to me at the Mayo Clinic by Dr Boothby,[18] but several similar cases seen in the Johns Hopkins Hospital have proven on subsequent postoperative follow-up examinations actually to be suffering from rheumatic mitral stenosis.

Auricular Fibrillation: Finally, in the still later stage, there appears auricular fibrillation with myocardial insufficiency, orthopnea, edema, enlarged liver, anasarca, and cardiac pain. Auricular flutter, heartblock, and bundle branch block* are forms of arrhythmia which also are seen occasionally. Electrocardiographic studies show the presence of the arrhythmias just mentioned and in earlier cases increase in the height of the T wave A direct relationship between the height of the T wave and the elevation of the basal metabolic rate has been traced in individual cases,[21] but this offers no particular help to the clinician. There may be electrocardiographic evidence of preponderance of one or the other ventricle, usually the left.

Among the cases which develop auricular fibrillation some show signs of congestive heart failure and others do not. Hamilton[22] has stressed this point and carefully described the clinical picture of those with congestive failure. He points out that in his series of fifty cases, exophthalmos was usually absent, the thyroid gland was often normal in size, and tremor and nervousness almost never occurred. In recognizing this form of congestive heart failure he stresses: (a) Tachycardia which does not respond as well as should be expected to complete rest and digitalization; (b) history of unexplained loss of about 13.6 kg. (30 pounds); (c) history of a surprisingly long duration of complete disability associated with gross signs of heart failure; (d) elevated B.M.R.** (he states that nonthyrotoxic congestive heart failure cases may have a B.M.R. of +63, which will return to normal when the heart failure is relieved).

It was pointed out in 1928[23] that nodular goiter with hyperthyroidism made itself apparent predominantly in individuals past the age of forty-five. In these individuals early degenerative changes in the myocardium coupled with deterioration in muscle tone from lack of active physical training provided an organism which was thought to be increasingly sensitive to thyroid secretion. Similarly, the average age of this series of Hamilton's cases was fifty years, and most of them were female patients. Thus, slight hyperthyroidism (so slight that the characteristic clinical signs of exophthalmos, goiter, tremor, and restlessness are hardly noticeable) could cause myocardial insufficiency in this group also Whatever theories may be held about these cases the fact remains that the best therapeutic solution lies in treating the hyperthyroidism. For this, if for no other reason, an element of "latent" thyrotoxicosis should always be suspected in an elderly individual who is suffering from congestive heart failure. In the nineteenth century it was fashionable to discuss these cases under the heading of Formes Frustes and more recently, cases have been described with normal metabolic rates who obtain symptomatic improvement from iodine medication or from subtotal thyroidectomy.

If thyrotoxicosis is brought to an end successfully, the heart returns to the condition it presented before hyperthyroidism occurred, if the condi-

* Only one case has been reported[20] in which the bundle branch block was abol[illegible]

** [illegible] an elevation of the [illegible] when patients are [illegible] leukemia or malignant tumor

tion runs on, death may eventuate, and in former days frequently resulted, from heart failure.*

In cases of hyperthyroidism showing simple tachycardia the operation for removal of part of the thyroid gland is followed in some cases by paroxysmal auricular fibrillation, which may last an hour or two or may go on for a day or two. Such a paroxysm usually stops spontaneously without harm, but the writer has seen cases in which emboli arose apparently from the fibrillating auricles. Previously it was thought that handling of the thyroid gland at operation might express an unusual amount of secretion into the general circulation, but the surgical methods in use today practically exclude this possibility. As the irritability of the heart muscle subsides after removal of the source of excess thyroxin the auricles usually revert spontaneously to normal contractions.

In his study of cases treated at the Johns Hopkins Hospital, Andrus[24] noted that auricular fibrillation in hyperthyroidism occurred only in patients over forty years of age or patients in whom the heart had suffered previous damage such as rheumatic valvular disease. The hearts of these patients, like those with nodular goiter with hyperthyroidism previously described, were less able to stand the overwork put upon the circulation in hyperthyroidism than are normal young hearts trained to compensate for constant excesses of physical exertion. It would appear then that one factor in the production of auricular fibrillation in hyperthyroidism is overwork, just as in cases of hypertension or mitral stenosis.

If auricular fibrillation in hyperthyroidism were purely a manifestation of the toxic effect of thyroxin on the heart muscle one would expect to encounter it more often in the fulminating severe cases of exophthalmic goiter of the young rather than in the relatively mild cases seen in the old As a matter of experience the reverse is the case. In an effort to explain this fact certain writers have hypothesized gradual myocardial damage occurring from long existing mild hyperthyroidism or even from nodular goiter without hyperthyroidism. The writer believes, rather, that a previously weakened or out-of-training heart by fibrillating brings to light a slight hyperthyroidism which otherwise would pass as symptomless Previously weakened hearts may fibrillate from the effect of mild or moderately severe thyrotoxicosis. Stroud speaks of coronary insufficiency in individuals past the third decade as playing a contributing part in the production of auricular fibrillation in patients with long-standing rheumatic valvular and myocardial damage. This change in the efficiency of the coronary circulation surely is an important factor in the development of auricular fibrillation in older patients with hyperthyroidism.

Nahum and Hoff[25] produced transient auricular fibrillation in four hyperthyroid patients with injections of acetyl-B-methylcholine chloride. [illegible] he action of a predisposing factor (E factor) [illegible] be produced by superimposed vagal stimu- [illegible][27] and auricular distention[28] also may act as predisposing factors. On the other hand, Surtshin and Rucknagel[29]

* Dr. J. Schranz, 1887: "Um das Herz dreht sich im der Regel bis zuletzt das Geschick des Kranken beim Kropf das degeneriete Herz bringt ihm den Tod"

failed to produce fibrillation with large intravenous doses of acetylcholine or methacholine in fourteen of fifteen experiments on dogs rendered hyperthyroid by feeding thyroid extract or injecting thyroxin intramuscularly They state, "The findings are interpreted as indicating that no increased cardiac sensitivity to vagus substance is present in canine experimental hyperthyroidism. Since, (a) the relation of age and sex to the incidence of auricular fibrillation in clinical hyperthyroidism resembles that of age and sex to the incidence of coronary atherosclerosis, (b) a large percentage of patients with hyperthyroidism and auricular fibrillation show evidence of organic heart disease, (c) no correlation exists between the height of the basal metabolic rate and incidence of auricular fibrillation in thyrotoxicosis, and in view of the experimental findings presented, it is suggested that the induction of auricular fibrillation in thyrotoxicosis is influenced by increased vagal activity in the presence of some state independent of the thyrotoxicosis. It is speculated that auricular ischemia may be conducive to the development of fibrillation and that coronary vascular disease, not necessarily progressive, may be present and favorable to initiation of the arrhythmia in a large fraction of the thyrotoxic patients with fibrillation, but no other evidence of organic heart disease."

The early stages of hyperthyroidism are quite indefinite and for this reason the resulting tachycardia may be indistinguishable from "effort syndrome" or "neurocirculatory asthenia." Estimation of the protein bound iodine in conjunction with the radioactive iodine uptake test usually dispells this confusion. In the later stages the thyroid factor in the cardiac derangement is quite obvious, although it is frequently difficult or impossible to estimate accurately the degree of underlying cardiac disease which may exist in addition.

Since 1933 Levine[10] has been interested in the occurrence of angina pectoris in patients with thyrotoxicosis. In 1950 he reported the association of these two conditions in twenty-four cases (eighteen men and six women). In this series angina pectoris decubitus was unusually frequent (seventy-five per cent) and the attacks of pain ceased promptly after the use of iodine preparatory to subtotal thyroidectomy. In this group clear-cut symptoms of thyrotoxicosis were fewer and less prominent than in patients with thyrotoxicosis without angina. They did well on treatment and one patient remained free from attacks of heart pain for as long as seventeen years. In this group the average age was fifty-four years and "in almost all cases the thyrotoxicosis had been overlooked because the two most obvious manifestations (enlarged thyroid gland and exophthalmos) were either absent or inconspicuous." He concluded that when coronary arteriosclerosis is present with thyrotoxicosis angina pectoris may be brought to light or aggravated by the increased demands on the heart.

From the foregoing description of the thyroid heart it will be seen that its chief characteristic is *tachycardia* which may progress, sooner or later, to auricular fibrillation. The mechanism producing the rapid heart rate still is not perfectly understood The older theories of cardiac embarrassment from mechanical pressure causing constriction of the trachea, or impaired blood flow through the cervical vessels, or irritation of the cardiac

nerves (vagus and accelerator) today have few advocates. What might be thought of as *subsidiary circulatory changes* that develop in hyperthyroidism have been measured by clinical and laboratory experiments. The blood volume is increased in hyperthyroidism and diminished in hypothyroidism,[31,32] the minute output of the heart is increased in hyperthyroidism,[33,34] and the blood flow is accelerated in hyperthyroidism and slowed in hypothyroidism.[35] The capillaries in the skin are constantly more dilated than in normal controls,[36] and Stewart and Evans,[37] in confirming these various findings in eighteen hyperthyroid patients, pointed out a lineal relationship between the rates of blood flow and basal metabolism. The blood flow changes in the skin provide for increased heat dissipation in hyperthyroidism and heat conservation in myxedema.[38] There is a marked similarity of circulatory change between the so-called beriberi heart and the thyroid heart and Means[39] believes that a relative vitamin B deficiency may develop in hyperthyroidism in the presence of the increase in metabolic demands.

Newer methods of studying cardiac output, blood flow, and other dynamics of circulation have been applied to hyper- and hypothyroid conditions.[40] Earlier observations that cardiac output is increased in hyperthyroidism even after congestive failure has developed have been confirmed by cardiac catheterization, and it has even been found that in some instances not only minute output but output per beat is increased. Usually, however, cardiac output increases proportionately with pulse rate and pulse rate with metabolic rate. Studies made in sixteen hyperthyroid patients[41] and two treated hyperthyroid patients to measure rate of removal from the blood stream by the liver of bromsulfalein by catheterization of the hepatic vein gave results, by applying the Fick principle, indicating that the hepatic blood flow is increased very slightly in hyperthyroidism and in some cases not at all, whereas the oxygen consumption of the liver is increased disproportionately.* The authors speculate as to whether this increased oxygen consumption with a normal blood flow might lead to anoxemia of the liver cells in the central portion of the lobule ultimately producing cellular damage. This would not, of course, account for the periportal fibrosis seen in some cases. Bromsulfalein retention was increased in some cases. In these same observations the systolic and mean blood pressures, but not the diastolic pressures, in the right ventricle and pulmonary artery were elevated, associated with an elevated pulmonary blood flow (cardiac output) and a normal pulmonary peripheral vascular resistance. Thus, a patient with thyrotoxicosis differs under conditions of exercise from the normal individual in whom the pulmonary blood flow can be doubled or trebled without any significant rise in pulmonary arterial pressure.

Other studies[43] made on nine patients with hyperthyroidism indicate that none of the cerebral metabolic functions varies significantly from the normal in this disease. Cerebral blood flow and oxygen utilization remain

* Further studies using improved technics which should give more accurate measurements may change these figures, but it seems probable that the basic facts will find confirmation.[42]

unchanged in hyperthyroidism, although cerebral blood flow and oxygen utilization had previously been shown to be lowered in myxedema. The renal blood flow is somewhat increased in hyperthyroidism and somewhat diminished in hypothyroidism.[44] Blood flow to the skin and muscles is greatly increased although oxygen utilization in skin and muscle is only moderately increased. Thus, the total arteriovenous oxygen difference actually represents an average of excessive rate of O_2 withdrawal in some tissues (splanchnic) and a reduced rate in others (muscles and skin).

Formerly it was believed that blood flow to an organ was regulated to adjust for the changing metabolic demands of that organ. This theory no longer is tenable. We see, for instance, that in hyperthyroidism the metabolic level in the liver is much higher than in other organs, yet the blood flow is roughly within normal limits. On the other hand, the metabolic rate in the brain is not increased nor is the blood flow altered. Peripheral blood flow is greatly increased and is out of proportion to increase in metabolism; and renal blood flow is moderately increased, although there is no evidence of increase in renal cell metabolic rate. The increase in cardiac output is greater proportionately than the total metabolic rate and one important function thus accomplished is to provide additionally blood flow for transport of body heat to the skin surface. Heat regulation depends in large measure on neurocirculatory reflexes.

From these observations one must assume that a major function of the increased blood flow in hyperthyroidism, which goes predominantly to the skin and skeletal muscles, is to provide for heat loss through the skin. Increased oxygen requirement may be satisfied, in the splanchnic organs, for instance, if not also in muscle, by more complete oxygen removal from the blood in passage.

Whether increased blood flow to the skeletal muscles is a merely necessary by-product of increase to the skin or whether, as seems more likely, it serves a useful function is not clear. Muscular weakness has long been recognized as part of the clinical picture of hyperthyroidism and Thorn[45] showed that creatinuria is a constant finding in these cases It has been thought[46] that this abnormal loss of creatine may constitute a step in lowering the labile phosphate supply and of the storage of the high energy phosphate compounds, creatine phosphate and adenosine triphosphate. Although the intimate action of thyroid hormone on cellular metabolism is not established, current concepts hold that it may act by uncoupling oxidative phosphorylation, leading to inefficient oxygen consumption and impaired use of energy sources important for contractile processes Thus, it is postulated that some such metabolic defect in the myocardium may contribute significantly to the development of heart failure when it occurs in thyrotoxicosis.

Although no final explanation of these circulatory changes is at hand, they all afford proof of the increased load borne by the heart in hyperthyroidism. The constant maintenance of a more rapid flow of an increased volume of blood by a heart whose muscle cell action is impaired and whose rapid rate robs it of most of its usual rest period during diastole constitutes a strain which challenges the underlying normality of the myocardium.

As throwing different light on thyroid tachycardia it is interesting to consider the effect of thyroid extract medication on cases of heartblock. Willius,[47] and Aub and Stern[48] have reported such observations and a similar case has been studied at the Johns Hopkins Hospital. Briefly the ventricular rate is unaffected by large doses (1.8 Gm. [28 grains] a day) of thyroid extract, although the body metabolism becomes elevated and the auricular rate increases as much as from 70 to 120. One must conclude that in the human organism either ventricular heart muscle is less sensitive to the direct action of thyroid extract than is auricular heart muscle with its delicate pacemaker, or that in the intact human being tachycardia is brought about through some indirect mechanism possibly mitigated through cerebral nuclei and the vagus and accelerator nerves. The later mechanism would fit more naturally into a homeostatic device than the former.

Conversely, experiments with isolated hearts from animals which have been rendered hyperthyroid by feeding with thyroid extract show that these heart muscle preparations maintain a rapid rate of contraction, 26 to 144 beats per minute faster than normal preparations under the same conditions for as long as ten hours after isolation.[49]

In an editorial discussion Andrus[50] in reviewing the literature says "Tachycardia and increased cardiac output at rest, exaggerated by exertion or excitement, regularly follow thyroid feeding or the injection of thyroxin in animals but only after a latent period of seven to twenty-four hours. Moreover, this effect may be produced in the embryo before the heart has been innervated or in the heart of one animal transplanted into the neck of another when the typical effects of thyroxin are produced in the host. Thyroxin has been shown to increase the rate of beating of explanted cardiac muscle cells from two day old chick embryos but only after twelve hours contact with the tissue. Tachycardia, once provoked in the intact animal by thyroid feeding or thyroxin injection, persists in the isolated perfused heart and increases far more than normal on addition of adrenalin to the perfusate. The denervated heart *in situ* in a hyperthyroid animal displays an exaggerated response to exercise or injected adrenalin.

"The oxygen consumption of the heart-lung preparation from thyroxinized animals is measurably increased as is the oxygen uptake of the isolated auricles from thyroxinized guinea pigs. It has been debated whether the increased rate of oxygen consumption can be accounted for by the increased heart rate. In the heart-lung preparation it seems that this may be so, but the oxygen consumption of the isolated auricle is measurably increased even though it fails to contract. In a few instances the oxygen consumption of that portion of the human heart drained by the coronary sinus (left ventricle) has been estimated by catheterization in the presence of hyperthyroidism, and found not to be notably abnormal.* In experi-

* When repeated by other investigators, however, the coronary blood flow in eight cases of hyperthyroidism was found significantly increased while the arteriovenous oxygen difference remained constant. Following effective treatment of the hyperthyroidism with I^{131} the cardiac output, cardiac work, coronary blood flow, and myocardial oxygen consumption returned to normal.[68]

mental hyperthyroidism, however, it seems certain that the cardiac tissue shares in the metabolic effect of the thyroid hormone, perhaps metabolic in nature upon the heart itself. In contrast, dinitrophenol, which notably stimulates metabolism, has much less influence on heart rate or none at all."

Although the exact mechanism by which these changes are brought about is still far from clear, the tachycardia, which is persistent and continues during sleep and is excessive after exercise, seems to be brought about by at least two mechanisms, (a) the homeostatic neurocirculatory mechanism thrown into action possibly by the increased heat production from elevated metabolic rate and (b) the direct effect of thyroid secretion on the heart muscle cells.

Dilatation and Hypertrophy: Whether or not dilatation and hypertrophy occur in an uncomplicated thyroid heart is still a disputed question. Those who think that hypertrophy of the ventricles occurs can find confirmation in the experiments on laboratory animals. Cameron and Carmichael,[51] in 1921 clearly produced hypertrophy of the heart in rats by feeding thyroid extract. In 1930 Simonds and Brandes[52] reported their work using dogs. They found that the hypertrophy involved all the chambers of the heart, with a slightly greater proportional increase in the left ventricle. Also, most accounts of the postmortem findings of the thyroid heart describe hypertrophy in a large number of cases, and of twenty-seven thyroid hearts studied in the Pathological Department of the Johns Hopkins Hospital by McEachern and Rake,[53] sixteen had definite hypertrophy. Lewis[54] reports twelve cases in all but three of which the heart weighed over 300 Gm. (10 ounces). Means and Richardson[39] also report the necropsy findings in twelve cases. Their series showed but little hypertrophy, and no important pathological changes were found at autopsy in a series of 18 dogs reported on by Rasmussen,[55] in circulatory failure with extreme tachycardia with diminished blood pressure and low cardiac output as a result of chronic thyroid intoxication.

The clinical evidence is not clear cut. Hurxthal[56] made careful cardiac measurements on thyroid patients before operation and again three months after operation. He found no contraction in the size of the heart, from which he inferred that there had been no previous enlargement He further compared 100 cases of toxic goiter with 100 cases of the nontoxic type and, after making correction for the transverse diameter of the chest and body weight, he concluded that the average transverse diameter of the heart in the toxic group exceeded that of the nontoxic group by only 0.49 cm. Friedberg and Sohval[57] (1937) reviewed the subject of cardiac hypertrophy in Graves disease. In twenty-seven fatal cases of hyperthyroidism studied at the Mt. Sinai Hospital hypertrophy was found in fourteen, but twelve of these suffered also from hypertension or severe coronary sclerosis or established auricular fibrillation. The remaining two cases showed hypertrophy of "very slight degree" independent of the various pathological states just mentioned. They believe that tachycardia compensates for increase in minute output of blood by the heart in hyperthyroidism and that the output per beat is not increased and therefore dilatation does not

occur in uncomplicated cases. Cardiac work is directly proportional, according to Starr,[58] to the pulse pressure. In hyperthyroidism this is increased. One would think this increased cardiac work would lead to hypertrophy, but since such is not the case there must be some additional necessary factor which is lacking in uncomplicated hyperthyroidism.

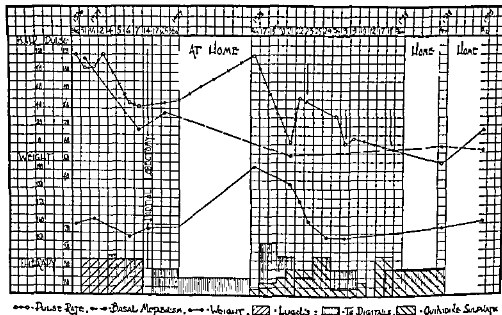


FIGURE 1. Case 1 Following the partial lobectomy the patient insisted on returning home before the auricular fibrillation had been interrupted During the thirteen months at home on digitalis, under the direction of his local physician, he continued to fibrillate and gradually went downhill During his second stay at the hospital on rest, digitalis and quinidine, he excreted 15 kg (33 pounds) of fluid in eight days and reverted to normal rhythm on the eighth day Since September 12, 1928, he has done full manual labor as a track man on the railroad without the loss of a single day from sickness and without taking either digitalis or quinidine (Thomas· Bull Johns Hopkins Hosp)

When congestive failure exists, from whatever combination of causes, dilatation of the ventricles occurs and this dilatation may disappear entirely when the hyperthyroidism has been allayed. The following case illustrates this statement.

CASE 1· Mr. G, aged forty-four years. Occupation: Railway track laborer. Admitted to the Church Home and Infirmary December 30, 1926.

Nervousness and prominence of the eyes had been first noticed about fourteen months before admission. Five months previous to admission (March, 1926) a local physician had diagnosed his case as exophthalmic goiter, but he was given no treatment. In April he suddenly lost his voice and this condition lasted three months after which it gradually disappeared. During the summer months the nervousness increased and he had several attacks of diarrhea His wife noticed that his appetite was abnormally good but that he was becoming tremulous About seven weeks before admission dyspnea, orthopnea, and palpitation became very marked and there was some cough and slight swelling of the ankles. There was no past history of tonsillitis, chorea, rheumatism, or

symptoms suggesting syphilis, the only previous illness being typhoid fever in 1916.

Physical examination: A well-developed man of forty-four years, weighing 72.7 kg. (160 pounds). He was very restless although not apprehensive His skin was flushed and moist. There was an extreme degree of exophthalmos of both eyes which had resulted in an inflammatory condition of the conjunctivae The thyroid was diffusely enlarged, rather soft in consistence with no thrills or bruits. Cardiac dulness measured 5 cm. to the right of the midline and about 9 cm. to the left. The sounds at the apex were quite irregular (108 to the minute) and a systolic murmur was heard. The sounds at the base were irregular; no murmurs. There was a pulse deficit of seventeen beats to the minute. Blood pressure 150/70 Lungs clear, no rales at the bases Liver not felt. Marked tremor of the extended fingers. Slight edema of the ankles.

Basal metabolic rate ninety-five per cent above the average normal for his size, age, and sex (December 31, 1926). Urine: Acid, 1 020, Alb. +, Sug 0, Micro: Normal Hemoglobin ninety-five per cent.

Course in hospital: Digitalis therapy was instituted and Lugol's solution, 0 6 cc. (10 minims), t i d. was given. Marked symptomatic improvement took place with a corresponding fall in the basal metabolic rate to +32 on January 6 (weight, 70 kg. [154 pounds]) and to +14 on January 11 (weight, 71.8 kg. [158 pounds]). On January 14 a subtotal thyroidectomy was performed by Dr. W. F. Rienhoff, Jr., without altering the patient's condition to any extent The Lugol's solution was discontinued (as is our usual procedure) and eleven days after the operation the B M.R. was +35 per cent. Auricular fibrillation persisted but the patient was forced to return to his home in West Virginia on January 26. From the history of his symptoms during the next twelve and one-half months it seems evident that auricular fibrillation persisted uninterruptedly He took tincture of digitalis under the direction of his local physician In May he resumed his work, but he could not do more than pump the handcar out to work and he often became short of breath. He was somewhat better during July, but in August he began to get nervous and run-down and could not walk 300 yards without breathlessness. He rested during September and improved slightly, but could only perform an occasional day's work during October, November, and December. Some time about the middle of December his condition began to go downhill and in February he noticed a good deal of swelling of the legs.

On his return to the hospital, February 15, 1928, he presented the picture of severe cardiac decompensation with auricular fibrillation, cardiac dulness 4 cm. to the right and 19 cm. to the left in the sixth intercostal space. Blood pressure 112/85. As the time the patient could stay in the hospital was extremely limited, digitalis and quinidine therapy were started simultaneously and eight days later, during which time he had lost 15 kg (33 pounds), the liver had become normal in size, and the pulse regular in force and rhythm. During the following week he continued to excrete the edematous fluid until at the end of fourteen days admission he had lost 19 kg. (42 pounds). Auricular fibrillation reappeared when the dose of quinidine was reduced, but normal rhythm was permanently restored by adding a dose of quinidine at midnight. The patient was discharged on March 24, 1928

He returned to Baltimore on June 7, 1928, for examination. He said that he had taken tincture of digitalis, 0 6 cc. (10 minims), t.i d and quinidine sulfate, 0 3 Gm. (5 grains), t i.d and at 11 P.M regularly, and had had no return of the irregular pulse. His strength had gradually increased so that he

felt he was ready to resume work. He looked quiet and strong. There was no edema; liver not palpable; no rales at the lung bases. Heart dulness 2 cm to the right and 13 cm to the left with a short, soft, systolic murmur heard at the apex. Sounds regular and of fair quality, although the first sound was somewhat muffled at the apex B M.R , −1 per cent. Weight, 71.3 kg. (157 pounds).

Electrocardiograph: June 7, 1928. Rate, 67; rhythm sinoauricular, P-R interval, 0.23 second T I, II and III inverted. The first degree heart block as well as inversion of T I and II and the sinus arrhythmia are almost certainly due to the amount of digitalis he has taken.

Teleoroentgenogram: MR 5, ML 9, T 30. Aorta slightly dilated.

The effect of exercise does not pass off as rapidly as is usual (pulse rate of 90 to 95, fifteen minutes after hopping fifty times).

The patient returned home, discontinued all medication and three weeks later began work in the garden He gradually increased his daily work until on September 12, 1928, he returned to his full work as a track man on the railroad. Since that time he has done full manual labor without the loss of a single day from sickness He arises at 5 A M., makes the fire, milks a cow; breakfast at 6, walks a mile to work which begins at 7:30 and lasts until 5; has a half hour for lunch During this time the work is fairly constant with a pick or shovel He usually returns home in a machine and retires at 8 P.M. He has noticed no swelling of the feet, no shortness of breath or irregularity of heart action, his appetite has been very good but not excessive and his weight has remained constant. At my request the patient returned for examination.

Physical examination: March 2, 1929—1 8 meters (5 feet 11 inches); 73 6 kg (162 pounds) There is quite definite exophthalmos, not as marked as on the previous examination, but still very evident. The sclera of the left eye is injected; conjunctivae not inflamed.

Thyroidectomy scar barely perceptible. No thyroid tissue felt

Lungs clear to percussion and auscultation; no rales at the apices or bases.

Heart: The apex is not clearly seen or felt. Dulness extends 8 cm. to the left of the midsternal line, 2 cm. to the right. No increase in dulness at the base. At the apex the sounds are clear, of good quality; no murmurs. No murmurs at the base.

Pulses are equal and synchronous and regular in force and rhythm; 17 to the quarter The vessel wall is not thickened; brachials not tortuous. Blood pressure 120/80.

Liver not felt nor enlarged to percussion. Spleen not felt.

Extemities: No edema of the ankles; no fine tremor of the fingers.

B M.R., −7 per cent.

Urine: Negative.

Electrocardiograph: March 2, 1929. Rate, 76. Rhythm sinoauricular, P-R interval 0 30 second. Remarks: T waves all upright P. II diphasic Diagnosis: Normal sinus rhythm.

Summary: A forty-four year old man suffering from diffuse goiter with hyperthyroidism complicated by auricular fibrillation and severe congestive heart failure was treated by iodine with reduction of the B M.R. from +95 per cent to +32 per cent followed by subtotal thyroidectomy. He insisted on returning home on the eleventh postoperative day before auricular fibrillation was relieved. Congestive failure and fibrillation treated with digitalis persisted for over a year when sinus rhythm was involved by quinidine. Following this

he gradually regained his strength and seven months la
manual labor. The heart had returned to normal size and
normal.

Pathological Changes: The first account to be given
changes in the heart of a patient who died of thyroid
Henry Marsh,[6] in a report before the Pathological So
1841. Before death, this patient had suffered from ir
and anasarca. The heart was greatly dilated, particular
showed some hypertrophy and granular fat along the r
valve. Since then various reports have been made noting
muscle and these reached their high point with Goodpa
two cases which showed degeneration and fragment
muscle fibers. Although Goodpasture was able to sh
cardium of thyroxinized animals was more susceptibl
injury from chloroform, he doubted that "products o
could be responsible for the cardiac lesions which may
in man in association with hyperthyroidism". Other
have failed to reveal any constant or clearly proven
in the heart which is definitely caused by hyperthyro

Clinically, it is thought that thyrotoxicosis produce
are permanent in their effect and patients are seen wh
years from the most extreme form of heart failure and
fect functional activity of the heart after subtotal thyr
in those patients who die quite evidently from hear
cardium frequently reveals no changes demonstrable by
pathological examinations. From a careful re-examinat
twenty-seven patients dying with hyperthyroidism at
Hospital it was concluded[33] that no pronounced pat
produced in the heart by hyperthyroidism. Current o
the hearts of patients dying from thyrotoxic heart failu
inconstant minor lesions, none of which can surely be
thyroidism. The changes most frequently encountered
dilatation and hyaline and fatty degeneration of the mu

CASE 2: N. C. Unit No. 7767. Johns Hopkins Hosp
Admitted September 22, 1926. Died September 23, 1926.

F. H.: Negative.

P. H.: Struma with no change in size for eighteen years

P. I.: Slight shortness of breath commencing seven mont
to be more prominent. Occasionally complained of pa
breakfast for husband this morning and seemed all ri
7 P.M. to find her in collapse—friends say that she wa
Sudden onset.

P. E.: P., 140. Apex rate, 240. T, 101. R., 60. Extrem
less, thrashing about, marked exophthalmos. Lids fail to
enlargement of thyroid. Lungs filled with rales. C. V.: A

Impression: Hyperthyroidism Exophthalmic goiter. Auricular fibrillaation. Myocardial failure.

Autopsy No. 9471: Thirty-two hours postmortem. The heart is enlarged and weighs 390 Gm. The right ventricle is dilated and hypertrophied, the left ventricle slightly hypertrophied Microscopically, there is definite perivascular and rather slighter intermuscular scarring especially toward the tip of the left ventricle. There is no cell infiltration The thyroid is adenomatous. The acini throughout appear normal, are colloid-cointaining and lined with cubical cells. There are some lymphoid nodules. The thymus is hyperplastic. Lung, spleen, and liver show chronic passive congestion. This is marked in the liver where there is central atrophy and necrosis.

Treatment: The treatment of the thyroid heart may be thought of quite simply in terms of protection of the patient as a whole until the improved modern technics of removing hyperthyroidism have prevailed. Thus attention should be focussed on avoiding harmful practices. Inept use of standard therapeutic procedures such as digitalization or the use of quinidine or adrenalin may prove disastrous. Relief of hyperthyroidism returns the heart to its previous more or less normal state.

When auricular fibrillation is present, digitalis usually exerts all of the benefits seen from this drug in other forms of auricular fibrillation. In some cases the slowing effect of digitalis is less marked than in cases of fibrillation uncomplicated by hyperthyroidism. When simple tachycardia alone exists, even though it may produce evidence of heart failure, the use of digitalis is without benefit and its use is strongly questioned by many. Dearing, Barnes, and Essex[61] produced round cell infiltration and areas of ischemia with toxic doses of digitalis in rats rendered hyperthyroid with thyroxin. No direct parallelism to human cases can be drawn from these experiments, but a sharp warning against over digitalization in hyperthyroidism is indicated. In the opinion of the writer it should be withheld until after operation or until some other indication for its use arises. For the same reasons venesection is rarely a helpful procedure.

After operation, quinidine is most valuable in obtaining reversion to normal rhythm in fibrillating hearts which do not revert spontaneously. It should not be used before operation because the slowing effect that digitalis has on the fibrillating heart is lost after normal rhythm is established by quinidine and dangerous tachycardia may ensue.

Symptomatic improvement is noted following treatment in an oxygen tent. When all is said and done, the ultimate and only lasting treatment is removal of the cause, that is, the hyperthyroidism. Subtotal thyroidectomy after preliminary medical treatment with an antithyroid drug and iodine is still the most widely used method to treatment.[62] With improved technic surgical mortality has become negligible (0.18 per cent at the Mayo Clinic) and end results greatly improved. Much of this improvement started with Plummer's[63] announcement in 1923 that iodine lessens toxicity in exophthalmic goiter. Iodine changed the patient into a good surgical risk, and the gland into a less hemorrhagic, less friable object for surgical removal. Then, with the advent of thiouracil and later the less toxic n-propyl-thiouracil and methyl-mercaptoimidazole (called tapazol or methimazole), the patient could be brought into a preoperative condition

of euthyroidism, and the gland, with the additional help of iodine, made to resemble a colloid goiter. The operation became less hurried and therefore more precise, more of the gland could be removed without danger to the recurrent laryngeal nerves or parathyroid glands, and thus fewer recurrences or persistences occurred after operation. Preoperative treatment could even be effected while the patient continued ambulant, and the operation performed on the second hospital day, the patient being discharged on the fourth to the tenth postoperative day.

The choice of anesthesia for thyroid operations in patients with heart failure deserves careful consideration. Because of the dangers of open drop ether anesthesia much attention was paid some years ago to developing a smooth local anesthesia method. With the improved methods of closed ether and oxygen anesthesia with gas induction the need for this has disappeared in all but the most desperately ill patients. Careful ether anesthesia preceded by light basal anesthesia or avertin or sodium amytal is the method preferred by Rienhoff in the Johns Hopkins Hospital. Lahey[64] advocates the use of cyclopropane combined with nitrous oxide since cyclopropane alone is likely to produce undesirable cardiac irregularities. The danger of bringing on these cardiac irregularities in offset, Lahey believes, by the absence of the excitement stage and of postoperative vomiting.

In some clinics sodium amytal (0.39 Gm. [6 grains] one hour before operation) and morphine (0.01 Gm. [1/6 grain] with strychnine 0.6 mg. [1/100 grain] a half hour before operation) are used as a basal anesthesia followed by ethylene in the operating room. We have encountered many hyperthyroid patients who were sensitive in one way or another to morphine and so we now take the precaution to give them a test dose several nights before the operation. Pantopon, 16 mg. (1/4 grain), can be substituted in sensitive individuals. Experienced anesthetists vary in their preference of methods depending on the technic with which they are most familiar. The combination ether method has the one indispensable advantage of keeping the depth of anesthesia constantly under control.

The surgical scar is scarcely visible. If myxedema threatens it can be perfectly controlled with desiccated thyroid gland. Instances in which the state of hyperthyroidism persists and becomes apparent after the effects of the antithyroid drug have fully worn off occur in only three or four per cent, and the other late complications of tetany or of recurrent-laryngeal-nerve palsy in only about one per cent. Tetany can be relieved by calcium, and the remaining normal vocal cord on the other side largely compensates for the paralyzed vocal cord. This method of treatment is so good, according to one of its proponents,[65] that it is unnecessary to look any farther, particularly if other methods may cause serious late complications from radioactivity and if many medically treated patients may still have to be operated upon.

There are, however, cases that are better treated by other measures. Prolonged medical treatment with antithyroid drugs such as propyl thiouracil or methimazole may be used to advantage in all mild cases and in severe cases that return promptly to a symptom-free state of euthyroidism,

provided the rare drug toxicities, such as agranulocytosis, are carefully watched for. Recurrent postoperative hyperthyroidism is often well treated in this way. It is of interest that young married women suffering from exophthalmic goiter who are maintained in a euthyroid state by daily doses of n-propyl-thiouracil not infrequently become pregnant whereas formerly the disease either prevented gestation or was terminated by surgical treatment. These patients can be carried through pregnancy on antithyroid medication. Preadolescent exophthalmic goiter responds in general to n-propyl-thiouracil as the adult form does.

Radioactive iodine (I^{131}) taken by mouth is utilized almost entirely by the thyroid gland, where it effects destruction of thyroid cells in proportion to its uptake. The dose is regulated according to the estimated size of the gland, 100 to 200 microcuries per gram of tissue, and although this is often little more than a rough guess it serves as an indicator for the size of the first of one, two, or rarely three doses. Shortly after the I^{131} is taken, the thyroid gland becomes slightly larger and tender and the patient more toxic, but this subsides within a few days or weeks; seventy-five per cent of patients become euthyroid after one dose at the end of several months, fifteen per cent require a second dose, and ten per cent need a third dose or more Nodular goiter with hyperthyroidism requires larger dosage and longer time to cure. In both types of hyperthyroidism the treatment extends over four to six months. Its advantages are that the patient need not be hospitalized (the drug is taken by mouth), parathyroid tetany and laryngeal paralysis do not occur (the gland is reduced usually to normal size), there is no operative mortality, and the cost to the patient is greatly reduced. Objections are theoretical, consisting mainly of the possible carcinogenic activity of the radioactive substance that remains in the thyroid gland until it loses its activity after a radioactive half-life of eight days. Thyroid cancer was induced in one and a half to two years in seven of twenty-five rats by a single intraperitoneal injection of 400 microcuries of I^{131}, and metastases were found in five;[66] the incidence of spontaneous cancer of the thyroid gland even in old rats was extremely low. After fifteen years of gradually increasing use of I^{131} in human patients with hyperthyroidism no case of malignant degeneration has been reported. Because of the possible late development of malignant degeneration some specialists prefer to use this form of treatment only in patients past forty years of age but do not hesitate to give it to younger patients who present clear-cut contraindications to surgical procedures. Its use is neutralized by previous absorption of iodine in any form. Thus iodine by mouth or in radio-opaque mixtures for x-ray series may block the uptake of I^{131} for weeks.

After this form of treatment myxedema develops in about the same percentage of patients as after surgical removal of the gland and is controlled by desiccated thyroid gland in the same manner. On the other hand, cases in which the hyperthyroidism persists or recurs at a later date are said to be less frequent, and when they do occur can be satisfactorily treated with further dosage of I^{131}.

Treatment in euthyroid patients of intractable angina pectoris or congestive heart failure by surgical or medical removal of the thyroid gland is described elsewhere in this volume.[67]

Conclusion: It may finally be concluded that the heart, in conjunction with the rest of the body, responds to hyperthyroidism by metabolic acceleration. This leads to a group of circulatory changes, the exact causes of which are only poorly understood. Tachycardia, increase in minute output of the heart, increase in blood flow to the skin and muscle but not to the brain and only slight to the kidney, acceleration of blood flow and increase in blood volume form a unique circulatory pattern which manages fairly well to care for the bodily needs of thyrotoxicosis and hyperthyroidism. Given a normal young cardiovascular system this speeding up does not overtax the heart and circulatory system. On the other hand when the heart is weakened by advancing age or heart disease the constant overwork combined with the direct effect on the myocardium from hyperthyroidism frequently leads to congestive heart failure and circulatory insufficiency. In either instance correction of the thyroid disorder allows the heart to regain, both functionally and structurally, its prehyperthyroid condition.

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13

The Heart in Anemia

The importance of any given factor in its relation to the heart and its physical and physiological integrity is immediately divisible into two issues. The first is concerned with the effects of the stress or noxious agent on the normal heart, and the second with these effects on the diseased heart or the heart laboring under an abnormal load: Hypertension and pregnancy or hyperthyroidism.

In 1857 Bamberger[1] reported his observation on patients having chronic anemia and concluded that cardiac enlargement was a frequent result. Irvine[2] in 1877 and Barrs[3] in 1891 described in chlorotic individuals the occurrence of bruits which were attributed to cardiac dilatation. Hersman[4] in 1893 described murmurs which disappeared with the cure of the anemia, and Gautier[5] in 1899 recorded his observations in twenty-two cases of chlorosis, and found, by percussion, cardiac enlargement in twenty. Cabot and Richardson[6] in 1919 found cardiac hypertrophy in patients dying of pernicious anemia, in whom no other factor existed to account for the enlargement Ball[7] in 1931 was apparently the first to report a case of severe anemia studied with the aid of a teleoroentgenogram, recording a reduction in heart size with relief of anemia.

Lunde and Schueller[8] in 1910 produced cardiac enlargement in dogs by rendering the animals anemic, and Forman and Daniels[9] in 1930, while studying the effects of certain food on anemia in rats, observed that the hearts of those animals having low hemoglobin values were considerably larger than the hearts of normal animals. When the hemoglobin values fell to 10 Gm., the hearts were slightly hypertrophied; this became marked as the degree of anemia increased. At the very low hemoglobin levels, from 2 Gm. to 3 Gm. per 100 cc., the hearts' weights averaged approximately three times those of normal animals Ellis and Faulkner[11] in 1939 reported the results from a study of forty-seven cases with varying degrees of anemia. Twenty of the thirty-eight cases studied by x-rays showed cardiac enlargement, and of the twenty-six who were followed, eighteen showed a decrease in heart size with improvement of the hemoglobin level. Ten of the forty-five patients studied by electrocardiogram showed abnormal records.

Recently much interest has been shown in the heart changes occurring in sickle-cell anemia. These changes manifest themselves by cardiac enlargement and murmurs; and owing to the bizarre joint symptoms, the

entire clinical picture closely mimics rheumatic fever with rheumatic heart disease. A study by Higgins and Toone is pertinent.[10]

From these reported observations one must conclude that protracted chronic anemias produce significant physical changes in the heart. In 1937 the writer[12] reported the heart changes occurring in hookworm

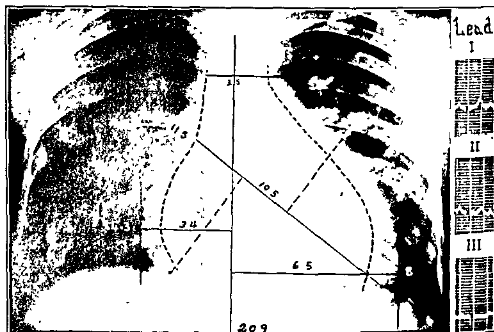


FIGURE 1*

Date	Hemoglobin Gm. per 100 cc	Cardiothoracic Ratio Predicted	Transverse Diameter Hodges and Eyster	Actual Transverse Diameter
4 to 18	1 4	58 8 per cent	Data incomplete	12 3 cm.
6 to 14	12 7	47 3 per cent		9 9 cm

Electrocardiogram: Sinus tachycardia; rate, 115; otherwise normal

anemia. It was realized that much information was available which dealt with the reaction of man to anemia, but the studies were concerned with relatively acute reductions in the oxygen carrying function of the blood; hence, the conclusions were applicable in only a limited degree to the changes developing in individuals with chronic anemia existing over periods of years. Many factors contribute to the physiological adjustments occurring in anemia of varying degrees, and duration, and the question was whether or not anatomical changes occur in the heart during the evolution of the compensatory processes.

The anemia associated with hookworm disease offered an ideal type of study. It varied in intensity, duration and rate of development, and was relievable by medication without the introduction of measures which might confuse the observations. In this study an increase in cardiac size

* See footnote, p 248

occurred in 100 per cent of the patients. The data indicated that the changes in heart size were in a few patients due to reducible dilatation (Fig. 1), in others to dilatation and hypertrophy (Fig. 2), and in a third group to definite hypertrophy unassociated with reducible dilatation (Fig. 3).

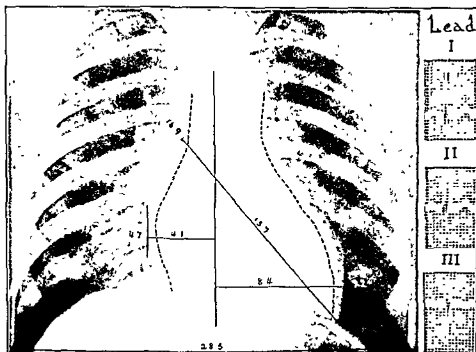


FIGURE 2*

Date	Hemoglobin Gm per 100 cc	Cardiothoracic Ratio Predicted	Transverse Diameter Hodges and Eyster	Actual Transverse Diameter
7 to 10	6 9	48 9 per cent	11 3 cm	13 9 cm.
8 to 16	9 5	43 8 per cent	11 4 cm	12 5 cm

Electrocardiogram Sinus rhythm; rate, 79, electrical axis, left preponderance

Cardiac hypertrophy is rightly placed in the category of organic heart disease; hence, one is justified in classing chronic anemia as one of the etiological factors in the causation of this condition. The primary cardiac dilatation may be classed as a physiological adjustment mechanism which disappears when the anemia is relieved; yet, if those factors which have necessitated the dilatation continue, there occurs hypertrophy of the myocardium which is not reducible and is definitely pathological in character.

The effects of chronic anemia on the diseased heart, or the heart under stress of hypertension, pregnancy or hyperthyroidism are of major clinical importance. The minute volume of blood handled by the heart is increased

* See footnote, p 248

by anemia, and the increase in cardiac output is definitely related to the degree of anemia. It is apparent, therefore, that anemia is an added drain on cardiac reserve in valvular heart disease and hypertension, and that it definitely augments the cardiac load of the pregnant woman and the patient with hyperthyroidism. This additional work not only augments

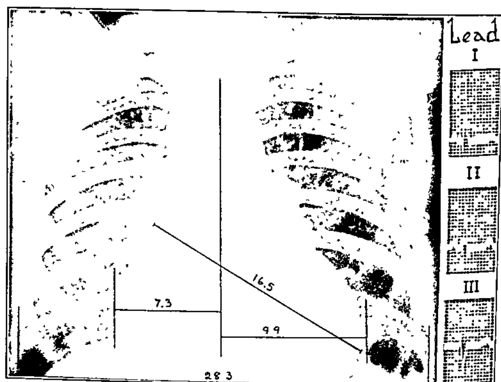


FIGURE 3*

Date	Hemoglobin Gm. per 100 cc	Cardiothoracic Ratio Predicted	Transverse Diameter Hodges and Eyster	Actual Transverse Diameter
7 to 3	4 9	60 0 per cent	11 3 cm.	17 2 cm.

7 to 29 death from intercurrent disease not related to the anemia Autopsy. Heart weight, 630 Gm ; otherwise normal.

Electrocardiogram: Sinus rhythm; rate, 70, electrical axis, left preponderance

the degree, but definitely accelerates the development of cardiac enlargement, and frequently precipitates premature heart failure.

Several authors have noted the occurrence of angina pectoris of effort in patients with anemia.[13,14,15,16,17,18] The specific nature of the angina syndrome has not been definitely settled, but it is universally agreed that it is concerned with cardiac work and oxygen supply.

When one studies a large number of patients with severe anemias, he is impressed by the fact that cardiac pain occurs only in the occasional

* All figures are composed of the first and last teleoroentgenograms; the latter is indicated by the dotted line. The outside figures represent the measurements in centimeters of the first and the inside figures of the last teleoroentgenogram. The hemoglobin values were obtained on the same day as the x-ray studies.

patient, and that the critical level for the anemia is quite variable Practically all of the reported instances have occurred in patients who are in the age group to quite logically have degenerated coronary arteries. The conclusion reached from a correlation of all the available facts is that the angina syndrome occurs in those anemic patients who have coronary artery disease. The degree of anemia necessary to precipitate the angina syndrome varies from case to case, depending upon the physiological integrity of the coronary arteries and this, in turn, is dependent upon the degree of coronary artery disease. It is doubtful if angina pectoris, regardless of the degree of anemia, ever occurs in patients with normal coronary arteries; yet, anemia can precipitate the angina syndrome in patients who have impairment of coronary circulation though no limitation of cardiac function be evident when the blood is normal.

CASE I: W. M., contractor, aged sixty. When first seen on September 6, he was complaining of substernal pain and oppression induced by slight exertion. He stated that his first symptoms were noted fourteen months previously, and that they were fatigue, slight dyspnea, and substernal oppression when he walked rapidly up slight inclines These symptoms had gradually increased in intensity until at this time he could not walk as much as a level city block without experiencing such intense substernal pain and oppression that he would be forced to rest Rest gave him complete relief.

Physical Examination The patient was a well-nourished man, weighing 196 pounds, five feet, ten inches in height. The mucous membranes and skin were manifestly pale and the tongue was smooth, clean, and the papillae atrophied. The heart was normal in size and shape, and there were no cardinal murmurs. The first sound was lacking in muscle tone, and the second aortic sound was amphoric and ringing in quality Pulse rate, 84, sinus rhythm The peripheral arteries and fundus vessels showed moderate sclerosis The blood pressure was 115 systolic and 85 diastolic The electrocardiogram showed moderate left axis deviation and an isoelectric T wave in Lead I.

Diagnosis: (1) Angina pectoris; (2) coronary sclerosis; (3) pernicious anemia.

Course and Treatment:

September 7—Hemoglobin, sixty-two per cent; RBC, 2,130,000.

September 8—Liver therapy begun

September 20—Hemoglobin, seventy-six per cent, RBC, 3,200,000 On this date he could walk on the level with comfort.

October 10—Hemoglobin, eighty-six per cent, RBC, 4,400,000 No symptoms with average physical activity.

November 2—Hemoglobin, ninety-four per cent, RBC, 5,120,000 No symptoms, and actively engaged in his vocation.

This patient was followed for three years There was a consistent recurrence of symptoms when the blood levels reached hemoglobin 70±, and RBC 3,000,000±. He died four years after we had first seem him of acute coronary occlusion.

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WILLIAM L. WINTERS, JR., M.D., AND
THOMAS M. DURANT, M.D.

14

The Heart in Pulmonary Disease

INTRODUCTION

Pulmonary disease as a specific cause for heart failure has become of considerable interest in recent years, and is becoming more frequently recognized. The development of right ventricular hypertrophy, dilatation and/or failure secondary to pulmonary artery hypertension resulting from intrinsic disease of the lungs or pulmonary vasculature has been designated "pulmonary heart disease" or "cor pulmonale." Prior to the introduction of these terms in 1931 by White,[121] "emphysema heart disease" was the designation commonly employed. With development of more precise methods for assessment of respiratory and circulatory function it has become obvious that "cor pulmonale" embraces a multitude of conditions having in common the development of right ventricular hypertrophy and failure. Considerable controversy remains as to whether pulmonary hypertension and right ventricular disease resulting from congenital anomalies or disturbances of function of the left side of the heart (mitral valve disease, left ventricular failure) should be included within the category of cor pulmonale.[18,43,48,77,95] It has been suggested that the terms *primary* and *secondary pulmonary hypertension* be used to differentiate between pulmonary and left-sided heart factors resulting in right-sided heart strain.[54]

Factors causing pulmonary hypertension may be classified into three groups:[24] (1) Factors affecting the pulmonary volume-elasticity relationship. These are anatomic or physiologic or both, and may consist of (a) a reduction in number, caliber and expansibility of the small vascular channels; (b) an increase in tone of the venules, arterioles or larger arteries; and (c) an increase in the pulmonary blood volume. (2) Factors affecting the flow-pressure relationship. An increase in blood flow causes pulmonary hypertension only if associated with any or several of the previous or following factors. (3) Factors causing an increase in left atrial and pulmonary venous pressure and volume. These may be due to (a) left ventricular failure, (b) mechanical obstruction at the mitral valve, or (c) changes in the volume-elasticity curve of the left atrium due to changes in its wall or in the pericardium.

The term *cor pulmonale* in this discussion will be restricted to etiologic factors affecting primarily the lungs or the pulmonary arterial tree and leading to pulmonary artery hypertension. Brief mention will be made of

Pages 251 to 270M replace former pages 251 to 270 © 1959

those factors which produce elevated pulmonary venous pressures with secondary elevation of pulmonary artery pressure.

The types of disease which may lead to the development of cor pulmonale may be divided conveniently into acute and chronic groups, the former developing after abrupt reduction of the pulmonary vascular bed, either in the absence of pulmonary disease (acute pulmonary embolization) or in the presence of acute infection superimposed upon chronic pulmonary disease. Chronic cor pulmonale presupposes the existence of chronic parenchymal or pulmonary vascular disease, with slow progressive development of pulmonary hypertension as demonstrable by clinical, electrocardiographic, radiologic or cardiac catheterization technics.

ACUTE PULMONARY HEART DISEASE

Etiology: The etiologic factors which have been incriminated in the production of acute pulmonary heart disease or acute cor pulmonale are:

- I Pulmonary embolization
  - A. Thrombi
  - B. Gas
  - C. Fat
  - D. Trophoblastic[2]
- II Pneumonectomy with thoracoplasty
- III. Acute infection superimposed on chronic pulmonary disease

By far the commonest cause for acute cor pulmonale is embolic blockage of the pulmonary circulation. Pulmonary emboli are found in 10 per cent of all autopsy subjects and are judged to have been the cause of death in 3 per cent of these.[78] Pulmonary emboli may arise in any part of the systemic venous circulation, with the exception of the portal system. The commonest sites of origin, however, are the deep calf veins and the veins of the pelvis, where thrombi are prone to form in postpartum and postoperative patients, or in patients long confined to bed for various medical conditions, e.g., a high incidence in those with heart disease.[64] Uncommonly, pulmonary emboli occur in apparently previously healthy individuals. Less frequently, emboli arise from vegetations on the valves of the right side of the heart, or from mural thrombi originating in the right atrium. Coronary occlusion may be complicated by pulmonary embolism when mural thrombi are dislodged from the endocardium overlying infarcted areas involving the right side of the interventricular septum. Only rarely do emboli arise from the upper extremities. The term *thromboembolic disease* is used to cover all aspects of these cases from the origin of the thrombi in the veins or heart to their lodgement in the pulmonary circulation. *Phlebothrombosis* denotes thrombus formation in veins without evidence of inflammation, in cont: [illegible] ch there is an inflammatory basis for the cl [illegible] ts are less frequent since the thrombus tends to be fixed at the site of origin. Stasis of blood within veins is an important factor in phlebothrombosis. This stasis is most often encouraged by confinement to bed which favors

pooling of blood in the calf muscles and pelvis and diminished muscle tonus (decreased efficiency of the circulatory "booster pumps"). One series reported that 50 per cent of autopsies of persons who had been confined to bed demonstrated venous thrombosis somewhere.[124] Various hematologic factors, such as increased numbers or enhanced agglutinability of platelets, hemoconcentration, increased thrombokinase, fibrinogen or globulin in the blood, and increased blood viscosity, may play important roles in the origin of intravascular clotting. Miscellaneous factors, such as age, weight and the presence of malignant disease, should also be mentioned. The vast majority of cases of thromboembolic disease occurs in persons past the age of forty years. In general the greater the age, the greater the tendency to this disease. Obese patients are more susceptible than those with normal weight, and those with malignant disease have an unexplained tendency to intravascular clotting.

Rarely, nonthrombotic emboli may produce the clinical picture of acute cor pulmonale. Either fat or air entering the systemic veins in sufficient amount may result in acute right-sided heart dilatation, circulatory failure, and death.

Not all pulmonary emboli produce the cardiac effect known as acute cor pulmonale. Very small emboli do not do so, and extremely large ones cause death before this effect is apparent. Between these extremes there is a considerable group of cases in which acute cor pulmonale is an important feature. It is highly doubtful that mere anatomic obstruction of pulmonary arteries or arterioles is sufficient to significantly raise pulmonary arterial pressures acutely to a degree capable of producing right-sided heart dilation. The normal pulmonary vascular bed has a large reserve. Normal pressure flow relationships can exist at rest with as little as one-third of the normal functioning lung volume. This is aptly demonstrated by surgical pneumonectomy which is rarely followed by pulmonary hypertension so long as the remaining lung is free of fibrosis, emphysema, or pulmonary vascular disease[25,43] Holden found it necessary to obstruct 70 per cent of the pulmonary circulation in dogs by massive pulmonary embolism before death occurred.[62] It seems probable, as suggested by Barnes,[7] that reflex spasm of the involved pulmonary circulatory bed markedly enhances the degree of circulatory obstruction caused by the embolus itself in these cases. Experimental studies by Price, Hata, and Smith support this impression.[99]

The studies of Fineberg and Wiggers have materially advanced the understanding of circulatory alterations and changes in right ventricular function which occur when there is obstruction in the pulmonary circulation comparable to that which exists in pulmonary embolism.[40] They demonstrated that the right ventricle of the dog is capable of maintaining its normal output if the pulmonary artery is compressed up to approximately 58 per cent of its original diameter. Under such circumstances the added resistance is overcome and the left ventricle receives its normal amount of blood. One factor shown to be of utmost importance in this compensation for added resistance is the increased initial tension and diastolic stretch of the right ventricle (Starling's law). Greater degrees

of compression of the pulmonary artery overwhelm the compensatory mechanism and there results a diminished transfer of blood to the left ventricle, a lowered aortic pressure, and a diminished coronary blood flow. There may be an additional humeral factor mediated by serotonin released from the blood clots in pulmonary embolism increasing vasodepressor reflexes and, in turn, potentiating a drop in systemic blood pressure.[112] The lowered blood supply to the myocardium undoubtedly plays an important role in the eventual complete failure of the right ventricle. Two deductions of therapeutic importance are made from these findings. The first concerns venesection which is to be condemned on the ground that lowering of venous pressure reduces the initial tension within the right ventricular cavity thereby interfering with the factor shown to be of such importance in the maintenance of normal blood flow to the left ventricle. The second concerns the importance of attempting to maintain an adequate arterial pressure and coronary flow to aid the right ventricle.

Acute cor pulmonale has been reported following pneumonectomy which was combined with thoracoplasty for pulmonary tuberculosis.[9] In the usual course of pneumonectomy, blood flow is readily channeled through dilated pre-existent vessels of hitherto nonfunctional capillaries.[25] If, however, sufficient emphysema or fibrosis in the remaining lung reduces the effective ventilation of that lung, anoxia results and contributes to elevation of pulmonary arterial pressures.

Less dramatic than pulmonary embolism, yet equally important in producing acute cor pulmonale, is acute respiratory infection superimposed on chronic lung disease (usually emphysema). This may occur in patients who have no evidence of chronic cor pulmonale. Emphysema and chronic bronchitis result in an inadequate bellows motion of the chest associated with improper alveolar distribution of gases and chronic alveolar hypoventilation. Superimposition of an acute infection upon this basic pathologic state leads to the abrupt development of anoxia. The latter is well known to aggravate pulmonary hypertension. In addition the infectious process may further decrease the pulmonary vascular bed and increase pulmonary resistance because of associated edema and exudate. Such a combination of acute anoxia and increased pulmonary vascular resistance has been reported capable of producing acute right-sided ventricular failure in an apparently previously normal heart.[10,114]

Clinical Features: The symptoms and signs of acute pulmonary heart disease will be considered along with those of the pulmonary embolism causing it, but special emphasis will be placed on the cardiac features[79] The size of the embolic occlusion determines to a large extent the character and severity of the symptoms and signs. A large embolus producing obstruction of a main pulmonary artery branch may result in sudden death. This tragedy may occur entirely without warning in a patient whose postoperative course has been apparently uneventful. In less severe cases, sudden intense dyspnea and a tightness in the chest or definite substernal pain are experienced. Peripheral vascular collapse often follows with a drop in systemic blood pressure, tachycardia with thready pulse, profuse cold perspiration, ashy pallor, apprehension, and nausea and vomiting. Less

common manifestations include cyanosis, syncope, convulsions, coma, and hiccough. Within the first hour or two, if death is averted, the manifestations of shock begin to abate, and the signs of right-sided heart strain, which constitute the acute pulmonary heart disease syndrome, become apparent. Dilatation of the chambers of the right side of the heart occurs, and the pulmonary conus region may impinge on the anterior chest wall, resulting in systolic pulsation in the pulmonary area. This impingement may also cause a friction rub audible along the left sternal border in the second, third, and fourth intercostal spaces, resembling a pulmonic systolic murmur. The increased pulmonary artery pressure is recognized clinically by accentuation of P_2 resulting from more forceful closure of the pulmonary valves. A gallop rhythm is frequently heard. Neck vein distention is prominent, reflecting the increase in venous pressure behind the dilated right ventricle. Marked pulsations in systemic veins indicate relative tricuspid insufficiency. Cyanosis which may not have been apparent in the shock stage is often now quite conspicuous. Gradual improvement may occur from this stage as right ventricular function returns toward normal, or progressive failure of the right ventricle terminating in death may prevail.

In twenty-four to forty-eight hours after the embolic episode, evidence of reaction in the lung itself appears. This is the stage of pulmonary infarction. Fever, tachycardia and tachypnea are present. The patients frequently lie on the affected side in an unconscious effort at splinting the involved pleura. Cough productive of bloody sputum is often present. Limitation of expansion of the involved side of the chest, dullness to percussion, increased fremitus, diminished breath sounds, and, occasionally, bronchial breathing may be noted. If the pleura is involved a pleural friction rub may be heard. Leukocytosis is present in 70 per cent of cases and increased serum bilirubin in 50 per cent. It should be emphasized that pulmonary signs and hemoptysis may at times be conspicuous by their absence.[79,124]

The cardiovascular effects of small emboli reaching the lung may be insufficient to produce this acute pattern or be so mild as to produce only pulmonary or pleural signs. On the other hand, unsuspected repetitious pulmonary embolization is becoming recognized as an important etiologic factor in the production of chronic cor pulmonale and at times closely resembles, clinically and pathologically, so-called primary pulmonary vascular hypertension.[6,7,8,29,88,96,97]

Roentgenologic Examination: Evidence of pulmonary embolization with or without infarction is usually absent in the early stages. The triangular or wedge-shaped radiopacity classically described with this condition is seen infrequently. The usual late finding in the presence of infarction is a shadow which has no pathognomonic characteristics[113] Plate-like atelectasis has been described as the most common finding.[124] Pulmonary arterial occlusion without infarction may be manifested by relative absence of vascular patterns of the involved side, termination of major arterial branches at the side of occlusion, or dilatation of the pulmonary artery proximal to the embolus. At fluoroscopy an overactive

pulmonary conus is often present and there may be noted a relatively immobile, high diaphragm on the involved side. An avascular lung distal to the obstructed pulmonary artery, simulating localized pulmonary emphysema, may be present. Angiocardiography may be of valuable assistance in localizing the areas of vascular obstruction. Lifesaving pulmonary embolectomies have been performed following such localization.[8]

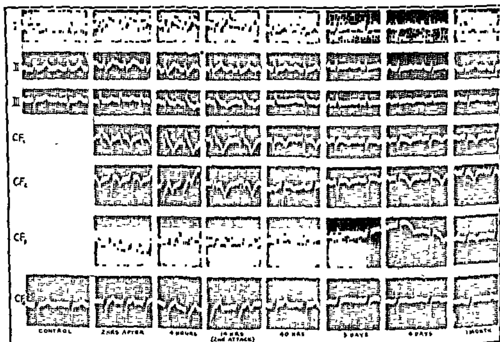


FIGURE 1 Postoperative pulmonary embolism Female, aged seventy-two First episode of embolism eighteen days following colostomy for adenocarcinoma of the rectum ... and four hours after ... rs after first. Electro- ... Note findings typical

Electrocardiogram: Electrocardiographic changes associated with pulmonary embolism constitute one of the extremely interesting aspects of the acute cor pulmonale. Changes are not present in all cases, but they do occur with sufficient frequency to be of great value. Diagnostic features are especially likely to be found when an electrocardiogram is taken within a few hours of the onset, and when other tracings are taken at short intervals thereafter, as in Figure 1. Such observations will show at least transient changes in 75 per cent of the cases.[124]

The electrocardiographic changes associated with the acute cor pulmonale are due to various factors, including rotation of the heart, myocardial ischemia, and probably pressure changes within the chambers of the right side of the heart.

With the advent of unipolar electrocardiography it was demonstrated that the heart rotates electrically on its long axis in a clockwise manner,

and on its transverse axis so that the apex is displaced backward [123] A tendency to a vertical electrical position (right axis deviation) also appears.[7] This results in the finding of an RS complex in the left arm unipolar lead, and a late R wave in the right arm derivation. In the standard leads a prominent S wave appears in Lead I (left arm minus right arm potentials), and a large Q wave in Lead III (left leg minus left arm potentials). Goldberger pointed out that the left leg unipolar lead does not show a significant Q wave as in infarction of the posterior wall of the heart.[60] This is of considerable importance in differential diagnosis In addition, the changes attributed to rotation of the heart tend to disappear within a few days of the onset of the acute cor pulmonale; whereas, the Q_3 pattern of posterior wall myocardial infarction persists.

Myocardial ischemia resulting from a markedly reduced coronary circulation pressure gradient (reduced aortic pressure together with a rise in coronary sinus and thebesian vein pressure) is responsible for significant ST-segment and T-wave changes in many cases. In the typical case, the ST segment is deviated downward in Leads I and II, and upward in Lead III. There tends to be a "staircase ascent" of the ST segment to an upright T wave in Leads I and II. In the unipolar extremity leads the ST segment may be elevated in the right arm (aV_R) and depressed in the left arm (aV_L) derivation In the precordial leads, ST-segment changes are minimal, though occasional depression is noted in the left-sided leads It is probable that the ischemia which accounts for these changes is predominantly that of the endocardial surface of the heart muscle.

T-wave inversion tends to occur in Lead III and in the right precordial leads [125] This association of T-wave inversion in Lead III with a large Q wave in the same lead is often mistaken for a posterior myocardial infarction. The absence, however, of a significant Q wave in the left leg unipolar lead (aV_F), the right precordial T-wave inversions, and the transient nature of the changes in the acute cor pulmonale will usually permit differentiation.

P-wave alterations are occasionally seen. Peaking of the P wave in Leads II, III, aV_F (P-pulmonale pattern) has been described, but similar findings are all too common in other circumstances to be of much significance.

Electrocardiograms taken within a few hours of onset of the acute cor pulmonale may demonstrate a transient right bundle branch block, complete or incomplete, which disappears quickly. This transient conduction disturbance is probably related to myocardial ischemia and the abrupt right ventricular cavitary pressure rise.[35] It is of interest to note that right ventricular conduction defects have been produced experimentally in animals in association with the marked right ventricular dilatation occurring with pulmonary (venous) air embolism.[36,92]

In a recent article an attempt has been made to group specific changes which may occur with pulmonary embolism into patterns which may have more diagnostic meaning Three common diagnostic patterns were delineated.[27]

1. $S_1Q_3T_3$, plus right precordial T-wave inversion

2. S_1T_3 or T_3 plus right precordial T-wave inversion.
3. $S_1Q_3T_3$ plus right bundle branch block.

Patterns *suggestive* of pulmonary embolism are:

1. Right precordial T-wave inversion alone.
2. $S_1Q_3T_3$ alone.
3. Right bundle branch block alone.
4. S_1T_3 or T_3 alone. T in lead aV_F often inverted also.

This study found the "staircase ascent" to be of little diagnostic value. Sinus tachycardia, the P-pulmonale pattern, clockwise rotation, and vertical electrical position were commonly present but of no diagnostic significance. Arrhythmias were uncommon.

Diagnosis: Clinically, the differential diagnosis of acute cor pulmonale resulting from pulmonary embolism may be difficult since acute myocardial infarction may mimic the signs and symptoms very closely. This differentiation may be exceptionally difficult in the middle-aged or elderly postoperative patient in whom either episode is not uncommon. Both acute cor pulmonale and coronary occlusion may be ushered in by sudden dyspnea, substernal chest pain, nausea, vomiting, and peripheral vascular collapse. Ashen pallor, cold perspiration, tachycardia, apprehension, and unconsciousness may appear in both. The friction rub of acute anterior myocardial infarction may closely simulate that due to the dilated pulmonary conus in pulmonary embolism. The aortic second sound is frequently diminished in myocardial infarction giving, at times, a false impression of accentuation of P_2 such as is heard with pulmonary embolism. Fever, leukocytosis, elevation of sedimentation rate are common to both. The more classical findings of pulmonary embolism include hemoptysis, pleural friction rub, and signs of pulmonary consolidation. These are usually lacking, however, in the early and quite often in the later stages. The electrocardiogram often provides diagnostic information, particularly if serial tracings are recorded. The introduction of serum enzyme determinations (serum glutamic oxaloacetic transaminase and serum pyruvic transaminase) has materially aided the clinician in resolving difficult problems. These enzymes are released into the blood stream by the destruction of myocardial cells in myocardial infarction in sufficient quantities to be of diagnostic importance, but no significant rise occurs in pulmonary embolism or pulmonary infarction.[68]

Treatment: The prevention of thrombus formation in the veins of the legs and pelvis, and hence, indirectly, the prevention of pulmonary embolism, is obviously the ideal in treatment. This should consist in an attempt to avoid, so far as possible, all the factors which are known to favor intravascular clotting. Venous stasis must be guarded against by the encouragement of deep breathing, by the prescribing of regular mild exercises and gentle massage for the feet and legs, and by the avoidance of positions in bed which will favor stagnation of blood in the pelvis and legs. Tight bandages applied to the abdomen may interfere with adequate respiration and increase venous pressure in the lower extremities, and should therefore be avoided. Excessive sedation, which inhibits both respiration and body movements, is dangerous.

There has been considerable debate regarding the advantages of early ambulation following operation. There can be no doubt that this procedure hastens recovery of the patient from his operative procedure, but it is not entirely certain as yet whether or not the incidence of phlebothrombosis and embolism is reduced thereby. Some statistics have indicated that there is no lessening of incidence but that the mortality from embolism is reduced. It is probably of utmost importance to recognize that, to be effective in this respect, early ambulation must mean not just sitting in a chair soon after the operation, but actual walking (with the aid of assistants, of course) in order to maintain muscle tone in the lower extremities and to prevent the occurrence of venous stasis.

Prophylactic bilateral superficial femoral vein ligation has been advocated by some for the prevention of postoperative thromboembolism in elderly patients. Experience, however, is accumulating which tends to indicate that embolism may still occur from thrombi which form at the point of ligation, and that there is little difference in the incidence of embolism in the ligated and nonligated groups of patients.

Anticoagulants, both heparin and Dicumarol, have likewise been tried prophylactically in patients following operation. Apparently the incidence of thromboembolism has been reduced thereby, particularly with heparin. There is reason to believe that Dicumarol does not have any significant anticoagulant action *in vivo* when dosage levels are maintained within a safe therapeutic range.[17] The danger of hemorrhage with any type of anticoagulant is a very real one, and it would appear that prophylactic use should be limited to cases in which there is great likelihood of abnormal blood coagulation. Heparin is the drug of choice for this purpose, but it should be discontinued preoperatively so that the coagulation time is restored to normal. Therapy should be reinstituted forty-eight hours postoperatively if no bleeding difficulty exists.

When signs of intravascular thrombosis, as indicated by a positive Homans' or Moses' sign, or by any other evidence, are detected by the physician, two courses of action to prevent embolism are open. Either the vein proximal to the thrombosis may be ligated or heparin therapy instituted, or both measures may be carried out simultaneously. There is an increasing tendency to rely on heparin alone in most clinics, but this anticoagulant should not be administered without coagulation time control of dosage, and there should be a full understanding of contraindications, dosage, and the therapy of bleeding should this occur.

If pulmonary embolism occurs despite all precautions, the physician is faced with a situation which constitutes, in many instances, one of the major emergencies of medical practice. Sometimes the patient dies immediately and there is no opportunity for therapy. Most often, however, the patient survives for a sufficient period of time to permit appropriate treatment to be instituted. It is essential to administer drugs which will tend to overcome unfavorable reflex phenomena which occur in association with pulmonary embolism and which add greatly to the circulatory difficulties. Atropine is of great value in this respect in that vasovagal phenomena are counteracted if the drug is given in sufficient dosage. The average

adult should receive 1 to 1.5 mg. intravenously to accomplish this purpose. Usually it is unnecessary to repeat this dose unless it is judged that a sufficient atropine effect has not been achieved, or unless repeated embolizations occur.

Another drug of definite value which may be given with the atropine, and which is probably the most important single agent in the attack upon this condition, is papaverine. This drug belongs to the benzyl-isoquinolin group of opium alkaloids, constituting about 1 per cent of the alkaloids of that narcotic. Its empirical formula is $C_{20}H_{21}NO_4$. While its discovery dates back to the work of Merck in 1848, its use in the treatment of pulmonary embolism was not reported until 1933.[30] A number of reports have since appeared, confirming its value. Experimental evidence has been presented by Megibow, Katz, and Feinstein[31(b)] demonstrating the pulmonary arterial dilating action of this drug both by means of radiopaque injection experiments, and by the discovery that, following the administration of the drug, there is a drop in the pulmonary diastolic pressure, despite a rise in systolic pressure, denoting a lessened resistance in the pulmonary arterial bed. Their evidence also indicates a very favorable central stimulating effect on respiration, an improvement in coronary flow, and a tendency to prevent ectopic rhythms which might lead to exodus in ventricular fibrillation.

The immediate administration of papaverine is therefore indicated in all cases of pulmonary embolism in which manifestations of the acute cor pulmonale are present. It should be given intravenously in a dose of 0.06 Gm. of papaverine hydrochloride injection, U.S.P. (1 cc. contains 0.03 Gm.). This dose may be repeated within an hour if necessary. The effect is prolonged, tending to last up to four hours. The onset of its action is rather slow, however, and it is for this reason that it is wise to administer it in the same injection with the rapidly acting atropine referred to previously. These drugs should be readily available in all hospital wards for the emergency situations which arise, not only in postoperative patients, but in medical cases as well.

Shock associated with pulmonary embolism should be treated by an intravenous drip containing amounts of l-norepinephrine adequate to maintain a systolic pressure of 100 (or, in the previously hypertensive patient, of 110), preferably introduced into the vein by way of a polyethylene catheter to avoid local ischemic effects. Digitalis is used whenever there is definite evidence of myocardial insufficiency with elevated venous pressure. Aminophylline may be given to those patients having bronchospasm, but it should be injected very slowly because of the danger of furthering peripheral vascular collapse. Oxygen inhalation is indicated in all cases. If heparin has not been administered before the attack, its administration should be instituted immediately in adequate dosage and with proper control of anticoagulant effect.

When pulmonary embolism and acute cor pulmonale result from gas which has gained entrance into the systemic veins, the maneuver of turning the patient onto his left side may be life-saving.[32] This should be

combined with artificial respiration and oxygen administration and, if need be, aspiration of the gas from the right ventricle.

CHRONIC PULMONARY HEART DISEASE

Incidence: Chronic pulmonary parenchymal disease per se, however extensive, does not necessarily imply eventual right ventricular hypertrophy, dilatation, or failure unless there is coincidental interference with the flow of blood through the pulmonary circuit.[13] This then represents a late development of chronic lung disease. Serious disturbances of cardiac function secondary to chronic pulmonary disease are therefore relatively uncommon. However, with employment of newer technics for comparing the ratio of right ventricular mass to left ventricular or left ventricular and septum mass, a higher necropsy incidence is being reported.[46,119] White and Jones reported an incidence of cor pulmonale of only 0.9 per cent of 2314 patients with organic heart disease studied by autopsy.[122] In contrast, Scott and Garvin found 6 3 per cent in 6548 necropsy subjects. This represented fifty cases in 890 cardiac patients of all types.[109] McKeown in 1952 reported 111 cases in 6770 necropsy subjects with evidence of right ventricular hypertrophy secondary to disease of the lungs.[81]

The incidence in relation to the type of pulmonary disease varies tremendously. Chronic cor pulmonale has been reported in 4 to 50 per cent of patients with pulmonary tuberculosis[55,118] Griggs and Coggin found 52 per cent of twenty-four patients with silicosis to have right ventricular failure[55] Wells found only four cases of cor pulmonale in necropsies of 388 coal workers with pneumoconiosis alone, but the incidence rose to 42 per cent in presence of emphysema and bronchiectasis[119] In all reports, chronic obstructive emphysema alone, or in combination with chronic asthma, bronchiectasis, or chronic bronchitis, constitutes by far the commonest cause of chronic pulmonary heart disease. Males outnumber females by 4 to 10·1.[45] The peak age incidence, weighted by the large numbers of chronic obstructive emphysema cases, ranges from the fifth to seventh decade.

Etiology: A convenient and simple classification of etiologic factors may be derived by dividing them into two categories: Group I—pulmonary diseases associated with chronic diffuse obstructive emphysema; Group II—pulmonary diseases in which the pathologic process primarily results in reduction of the pulmonary vascular bed or reduction in transfer of gases across the capillary membrane. It must be understood that these two groups are not rigidly exclusive and frequently coexist.[77]

Group I· Chronic obstructive emphysema with alveolar hypoventilation and hypoxia

- A Chronic bronchitis
- B. Bronchial asthma
- C Bronchiectasis
- D Bullous emphysema[4 33,44]
- E Restrictive diseases of the chest
  1. Kyphoscoliosis

2 Pectus excavatum
3. Fibrothorax

F. Obesity syndrome
G. Pulmonary tuberculosis with obstructive emphysema
H. Sarcoidosis with obstructive emphysema
I. Silicosis with obstructive emphysema

Group II: Pulmonary disease with predominant reduction in the pulmonary vascular bed

A. Intraluminal processes
1. Primary pulmonary hypertension
2. Chronic recurrent pulmonary emboli
3. Chronic massive pulmonary thrombosis
4. Schistosomiasis
5. Syphilis of the pulmonary arteries
6. Sickle cell anemia

B. Extraluminal processes
1 Granulomatosis
a. Sarcoidosis with interstitial granulomata
b. Berylliosis
2. Interstitial fibrosis
a Hamman-Rich syndrome
b Silicosis
c Lymphangitic or metastatic carcinomatosis[76]
d Chronic obstructive or bullous emphysema
e Scleroderma
f Pneumoconiosis (anthracosilicosis)
g Rheumatic pneumonitis
h Polyarteritis nodosa
i Diffuse interstitial fibrosis of unknown etiology
j. Celiac disease with emphysema
k. Congenital cysts of lung
l Diffuse infiltration by bronchogenic carcinoma[53]

The physiologic and pathologic disturbances resulting in pulmonary hypertension in these entities will be discussed in the following section.

Pathogenesis: The development of pulmonary hypertension can be traced to one or more of four basic causes:

1 Increase in pulmonary blood flow. In the normal state, pulmonary flow may be increased three to four times without a change in pulmonary artery pressure (30/4-12) or arteriolar resistance (less than 200 dynes per second per centimeter^{-5}). This is accomplished by the great distensibility of the pulmonary tree, and the opening up of numerous unused reserve capillary channels to handle the excess flow. Pulmonary hypertension due to increased flow per se is not usually met with in pulmonary disease until the vascular bed is reduced.[28]

2. Restriction of the pulmonary vascular bed. This usually takes place at the level of the small arterioles or capillaries secondary either to arteriolar spasm or organic arteriolar changes which raise pulmonary arteriolar resistance.

3. Anoxia or hypoxia. The importance of anoxia in elevating pulmo-

nary artery pressures and resistance by the vasoconstriction of pulmonary vessels has been clearly demonstrated.[42,85,115]

4. Elevation of left atrial pressures due to disease or insufficiency of the left side of the heart. This secondarily produces elevation of pulmonary arteriolar resistance.

It is apparent that when right-sided heart failure makes its appearance in chronic cor pulmonale it is fundamentally the result of an excessive work load from long-standing elevation of pulmonary arteriolar and total pulmonary resistances.[43] Other factors, however, are involved.

In *Group I*, fixed structural changes in the pulmonary vascular bed were formerly believed responsible for the increased pulmonary pressures.[86] But with the advent of cardiac catheterization such elevations were found at times to be both transient and reversible.[87] Structural changes, therefore, cannot be the whole story. Emphysema primarily disturbs pulmonary function by impeding air flow in and out of the lungs. There is a marked increase in total residual volume and reduction in maximum ventilatory and timed vital capacities. There is uneven distribution of air in the alveoli and this, in turn, produces uneven distribution of aeration of blood. When this process progresses sufficiently to reduce systemic arterial oxygen saturation, further changes occur. A direct hypoxic stimulation of the bone marrow presumably stimulates a secondary type of polycythemia. This is associated with an increased blood viscosity and blood volume, increased venous return, increased cardiac output, and a residual volume of blood in the lungs. These changes in the presence of a decreased pulmonary vascular capacity result in a further increase in pulmonary artery pressure. Hypoxia itself increases cardiac output[60] and by direct action on pulmonary vessels affects a reduction in their caliber.[56,59,115] Eventually, reduction of the vascular bed occurs through rupture of interalveolar septa with loss of capillary bed, replacement of normal tissue by relatively avascular fibrosis, compression of vessels by atelectasis, inflammatory exudate, and fibrosis. Long-standing increased intravascular pressure produces secondary changes consisting of endarteritis obliterans, medial hypertrophy, intimal fibrosis, endothelial proliferation, and eventual pulmonary atherosclerosis.[15] These changes add also to the pulmonary resistance. The vascular impedance, however, is a late development in chronic emphysema. It is felt that the most important factor in the development of the cor pulmonale is the hypoxia which in many instances is reversible and therefore of utmost importance to recognize.[77]

The optimal stretch of the myocardial fibers is exceeded and right ventricular failure occurs[24] through the combination of these separate factors: (a) increased blood volume, (b) high cardiac output, and (c) direct action of anoxia on the strained right ventricular myocardium, possibly a reduced vascular bed, and marked pulmonary hypertension. This failure is characterized by an impairment in the emptying of the right ventricle, increase in right ventricular diastolic volume, and elevation of end diastolic filling pressure. If proper therapy is instituted this type of failure is usually easily correctable as there is little evidence for intrinsic myocardial disease and the coronary blood flow is reportedly normal.[103]

Specific mention should be made of several of the less common entities in Group I. Fatal cardiac failure resulting from chronic cor pulmonale in individuals with thoracic deformities is relatively rare. Kyphosis, kyphoscoliosis and pectus excavatum are the common deformities involved. In 30,729 necropsies performed at Cook County Hospital only 11 cases (0.036 per cent) fitting this classification were found.[41] Such patients are prone to pulmonary infections. All show varying degrees of atelectasis, bronchiectasis, chronic bronchitis, and compensatory or obstructive em-

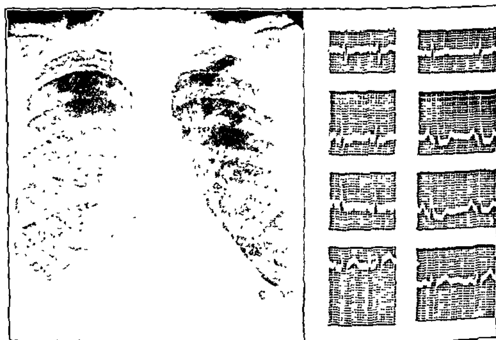


FIGURE 2 Chest x-rays and electrocardiograms of a sixty-three year old male with pulmonary tuberculosis and right-sided heart failure The x-rays demonstrate the bilateral *fibroid tuberculous lesion with spontaneous pneumothorax* or large [illegible] The first electrocardio- [illegible] one year of observation (Temple University Hospital case)

physema. Their respiratory mechanics are inefficient, resulting in compensatory hyperventilation. Eventually in the third to fourth decade the ventilatory capacity and respiratory gas exchanges are so reduced that hypoxia and carbon dioxide retention set in motion the cycle previously described.[18,53,126]

A recent entity colorfully entitled the "Pickwickian syndrome"[14] has been described in detail.[23,37,71,111] It is characterized by extreme obesity, somnolence, periodic breathing, cyanosis, polycythemia, right axis deviation shown in the electrocardiogram, and congestive heart failure. Physi-

ologically there are found decreased vital capacity, expiratory reserve volume, functional residual capacity, tidal volume, and total minute volume. Distribution and diffusion of gases within the lung are normal. The physiologic dead space is increased. The major physiologic abnormality is inadequate alveolar ventilation resulting in arterial oxygen unsaturation and carbon dioxide retention. The reason for alveolar hypoventilation has not been conclusively explained, but is presumably due to the tremendous abdominal girth and fat deposits on the chest wall which permit only shallow diaphragmatic breathing.[1,14,26] Despite maintenance of minute volume by increased respiratory rate, a point is reached where the tidal volume falls so low that alveolar hypoventilation occurs. The hypoxia presumably initiates the cycle of polycythemia, hypervolemia, pulmonary hypertension, and right-sided heart failure. The entire syndrome is reversible by weight reduction.

There is no agreement as to the frequency with which right ventricular hypertrophy occurs in association with pulmonary tuberculosis. Nemet and Rosenblatt[90] reported exclusive hypertrophy of the right ventricle in 33.8 per cent of seventy-one pulmonary tuberculosis patients studied postmortem. On the other hand, Griggs, Coggins, and Evans[55] found only 3.7 per cent of pure right ventricular hypertrophy in 1470 patients with tuberculosis uncomplicated by other pulmonary disease. This latter finding is in better accord with the general opinion on this subject. When congestive heart failure occurs it is usually in patients with advanced bilateral disease. In this instance, emphysema accompanied by severe fibrosis and reduction in pulmonary vascular bed usually coexists. The roentgenogram and electrocardiograms from an illustrative case are reproduced in Figure 2.

In *Group II*, reduction in the pulmonary vascular bed by pulmonary parenchymal disease or conditions localized mainly in or about the pulmonary vessels may be the initiating factor in the development of chronic pulmonary heart disease. In most of these cases, hypoxemia is not a factor early in the course and does not play a major role in the development of pulmonary hypertension as it does in the first group. In the earlier stages, pulmonary hypertension occurs only during exercise when the increased blood flow does not have access to reserve channels present in the normal lung. As the vascular bed is further restricted, hypertension develops even at rest. If the patient does not die of pulmonary insufficiency he will eventually develop anoxemia, first with exercise, then at rest. This anoxemia is thought to result from three factors: (1) Alveolar-capillary block occurs in patients with granulomatosis and diffuse interstitial fibrotic lesions. (2) The factor of "contact time" is of importance in many cases.[74] To maintain a specific volume flow through a restricted vascular bed, the rate of flow must increase with exercise. At a critical level the flow becomes so rapid that alveoli and blood are not in contact sufficiently long for diffusion of gases This results in a widened alveolar-arteriole oxygen tension gradient and unsaturation of arterial blood. (3) Emphysema often accompanies the extra luminal processes and results in the cycle of events previously described.

Since, in the earlier stages of this group, the factors of anoxia and hypervolemia play a small role, no stage of high cardiac output precedes the eventual cardiac failure. When failure does develop it may be precipitated by acute anoxia (due often to superimposed acute infection), and it is characterized by diminished cardiac output and irreversibility. The latter is dependent on pathologic changes which cannot be altered therapeutically.

The specific diseases form a diversified group. Of those involving primarily the pulmonary arterial tree the most controversial is primary pulmonary hypertension. It has been variously described under headings such as primary pulmonary vascular sclerosis, idiopathic pulmonary hypertension, right ventricular hypertrophy of unknown origin, Ayerza's syndrome, cardiacos negros, and many others.[17] The question as to whether this syndrome actually exists has not been conclusively settled. It is defined by Dresdale[34] as an elevation of pulmonary artery pressure with right ventricular hypertrophy whether or not associated with pulmonary vascular sclerosis McGuire[80] restricts the definition to right ventricular hypertrophy and pulmonary artery hypertension in the complete absence of other cardiac or pulmonary vascular disease. The nature, distribution, and severity of the pulmonary vascular changes proximal to the capillary bed vary considerably in those cases where changes are reported to have been present.[38,61,110] These changes embrace atheromatous plaques of the stem and large elastic arteries alone or in conjunction with fibrous intimal thickening and narrowing of the smaller arteries and arterioles, medial hypertrophy, intimal sclerosis, and thrombi in various stages of organization.[15,34,105] Whether the obliterative sclerosis or thrombosis is the cause or effect of the pulmonary hypertension has evoked considerable argument. It is pointed out that these intimal changes are indistinguishable from those seen with recurrent pulmonary emboli. The primary factor in producing hypertension in those with predominant medial hypertrophy has been suggested to be the persistence of fetal type pulmonary arterial tree.[15] The clinical course is characterized by its appearance in the younger age group of forty to sixty years, with a predominance of females (60 per cent). Exertional dyspnea, effort syncope, chest pain closely resembling that of angina pectoris, and varying degrees of cyanosis without clubbing of the fingers are of special importance. There is usually a rapid downhill course lasting five to sixty months terminating in right ventricular failure and occasionally in sudden death. Deaths have been reported following Decholin circulation time determination and cardiac catheterization.[105]

The term "Ayerza's disease" was originally popularized by three students of Ayerza in describing a condition characterized by severe cyanosis and polycythemia (cardiacos negros) associated with pulmonary disease. The condition was presumed to be of syphilitic origin.[70] Since then, however, the designation has been used to describe primary pulmonary hypertension, severe obstructive emphysema with pulmonary arteriosclerosis, and a host of other diseases characterized by pulmonary arteriosclerosis, hypertension, cyanosis, and right-sided heart failure. It would be best to drop this term from general usage.

In experimental animals, vascular sclerosis closely resembling that seen in the syndrome of primary pulmonary hypertension has been produced by repeated pulmonary embolization with fibrin, blood clots, and amniotic fluid.[106] The histologic reaction is primarily confined, however, to the intima with a normal or atrophic medial coat.[6,34,58] The clinical counterpart is being recognized with increasing frequency. Pulmonary emboli, either recognized or unrecognized clinically, are now a well-established cause for the development of chronic pulmonary heart disease.[6,21,29,96]

Chronic massive main or stem pulmonary artery thrombosis has also been incriminated.[8,16,66,98,101,104] This was reported either in conjunction with pulmonary embolication or chronic pulmonary disease or both. Survival in the face of main stem thrombosis is permitted through rapid expansion of bronchial-pulmonary artery anastomoses. Venous angiocardiography will readily demonstrate the presence of such a thrombosis.[57]

Pulmonary thrombosis and infarction occurring in a patient with sickle cell anemia are suggested by episodes of chest pain, unexplained dyspnea, or pneumonitis.[84] Repeated infarctions in the sickle cell state may lead to chronic cor pulmonale though considerable reduction of the pulmonary vascular bed must occur. This complication is most apt to develop in the presence of severe anemia, a high percentage of S hemoglobin, frequent pulmonary infections, and sudden demands for greater oxygen utilization. These states may initiate sickle crises with subsequent intravascular thrombosis.

In areas of the world where schistosomiasis is endemic, cor pulmonale may be found in 2 to 5 per cent of patients harboring this parasite.[49] It is usually a complication of Schistosoma hepatic cirrhosis. The pathologic picture is one of relapsing endarteritis of serous, fibrinous, and hemorrhagic types in small arterioles, thrombus formation, pseudoaneurysms, and angiomatoid structures.[72] Except for the latter which are quite characteristic of this disease, the changes are similar to those which may be seen in rheumatic fever, thromboangiitis obliterans, and polyarteritis nodosa.[73] The exact mechanism for production of this arteritis is unknown It is presumed to be the result of (1) an allergic reaction to toxins elaborated by the Schistosoma ova, or (2) granulomatous reaction within or around the obstructed arteriole secondary to the physical presence of the ova. The development of right-sided heart failure in these patients is an ominous sign and is usually followed by cyanosis. Abrupt termination of the illness in death is to be expected at this stage.

Syphilis of the pulmonary arteries is an extremely rare condition. Brenner reports that there are only fourteen cases reported in the literature in which the diagnosis is reasonably well proved.[12]

The group of diseases listed under the extraluminal processes in Group II all have in common the production of diffuse interstitial fibrosis or granuloma Only occasionally is the extent of the granulomata of sarcoidosis and berylliosis sufficient to reduce the pulmonary vascular bed to an extent capable of elevating pulmonary artery pressure.

Anthracosilicosis is frequently the cause of pulmonary heart disease in mining regions where anthracosilicosis, rather than pure silicosis, occurs.

Pure silicosis leads to early disability and death from silicotuberculosis, thus allowing insufficient time for the development of cardiac manifestations. A valuable statistical study of this subject is that of Coggin, Griggs, and Stilson[20] who found right ventricular hypertrophy to be present at autopsy in approximately one-half of 102 pneumoconiosis patients. Definite congestive failure was more frequent in these subjects (51 per cent) than was tuberculosis (41 per cent). Wells corroborated these findings in 1954.[119] In 136 patients with massive pneumoconiosis, autopsy showed that 42 per cent had chronic pulmonary heart disease without evidence of left-sided heart disease. But of seventy-one patients with pneumoconiosis plus tuberculosis only 17 per cent died of pulmonary heart disease (Figure 3).



FIGURE 3 Chest x-rays and electrocardiogram of a fifty-eight year old male with advanced anthracosilicosis and chronic pulmonary heart disease. Enlarged pulmonary conus indicated on x-ray by arrow. Electrocardiogram shows normal axis with large, broad P waves in Leads II and III. Tests of circulatory function in this case indicated incipient right-sided heart failure Death resulted, however, not from congestive failure, but from acute miliary tuberculosis which developed a few weeks after the above x-rays were taken. (Temple University Hospital case)

Broadly speaking, the "collagen diseases" are capable of producing interstitial pulmonary fibrosis as well as pulmonary arterial changes and rarely pulmonary heart disease.[32] In scleroderma there may be found large irregular masses of fibrosis or diffuse fibrosis with cystic formation.[91] Lupus erythematosus produces nonspecific changes of bronchopneumonia, edema, and occasionally alveolar fibrinoid degeneration as well as the better-known vascular changes. Polyarteritis is characterized by a necrotizing arteritis. Rheumatoid arthritis may be associated with pulmonary fibrosis—either localized or diffuse. Special mention should be made of

rheumatic pneumonitis. Patients who have suffered from long-standing rheumatic infection frequently present, in addition to chronic damage of the heart valves, an interstitial pneumonitis with hyperplasia of elastic tissue. Previously it was assumed that this change in the lungs was a result of long-standing pulmonary congestion due to mitral stenosis. The studies of Gouley[52] have shown, however, that while congestion intensifies the fibrosis in the lungs, it is only a secondary factor in the production of fibrotic changes. Primarily involved is a chronic rheumatic interstitial pneumonitis which, like rheumatic myocarditis, is often accompanied by evidence of recurrent inflammation. Histologic changes consist of alveolar lining cell proliferation, organization of exudate, fibrinoid necrosis of bronchiolar lamina propria and arteritis.[75] The right-sided heart failure which characteristically terminates rheumatic heart disease may then result, at least in part, from fibrotic pulmonary disease. Gouley has shown that such failure may occur even in the absence of significant mitral valvular dysfunction. Such cases as these could be correctly classified, then, as examples of pulmonary heart disease of rheumatic origin.

In summary, a schematic diagram is presented (Figure 4) to illustrate the general principles involved in the development of pulmonary heart disease.[28]

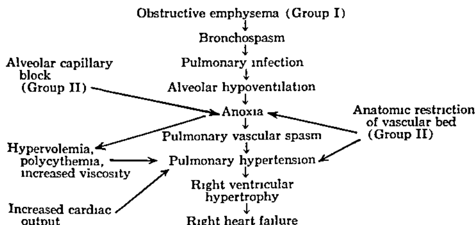


FIGURE 4 General principles in development of pulmonary heart disease

Clinical Features: The diagnosis of chronic cor pulmonale would be made irregularly if reliance were placed solely on the demonstration of right ventricular hypertrophy since early detection of such hypertrophy is extremely difficult. A high index of suspicion must be maintained, therefore, to correlate all suggestive evidence so that a presumptive diagnosis may be made before marked progression of the disease has occurred

The symptoms and signs of chronic pulmonary heart disease are, first, those associated with the primary pulmonary disease; and, second, those produced by the cardiac dysfunction. The pulmonary symptoms and signs need not be discussed in this chapter, since such a discussion would be beyond the scope of this book. It must be emphasized, however, that

TABLE I

	J B —Male, 57	I M —Female, 46	J R —Male, 20	Normal Value
History	Increasing dyspnea for 1 mo		Progressive dyspnea for 6 months	
Respiratory rate	19/min	23/min	14/min	15-20/min
Minute volume	8 87 L /min.	13 8 L /min	16 6 L /min	6-12 L /min.
Tidal volume	466 cc	602 cc.	1188 cc.	500-1000 cc
Inspiratory capacity	1850 cc	900 cc	1850 cc	
Expiratory Respiratory Volume	800 cc	400 cc	1550 cc.	
Vital capacity				
Standing	2550 cc	1500 cc	3550 cc	2500-4000 cc
Predicted	3690 cc.	2855 cc	4320 cc	
Percentage of predicted	69	52	82	100
Maximum breathing capacity	39 9 L/min.	113 1 L /min	64 3 L /min	
Predicted	94 0 L/min.	79 0 L /min	121 0 L /min	80-130 L /min.
Percentage of predicted	42	157	53	100
Timed vital capacity				
1 second	14%			
3 seconds	50%	100%		
Saturation arterial	88%		100%	100%
Hemoglobin	17.3 Gm. %	94 4%	96 0%	94-97%
Hematocrit	52	Normal	Normal	
Diagnosis	Chronic obstructive pulmonary emphysema; early cor pulmonale; maximum breathing capacity reduced out of proportion to vital capacity; timed vital capacity markedly delayed, early polycythemia.	Hamman-Rich syndrome; alveolocapillary block; restrictive pulmonary disease; chronic cor pulmonale; inspiratory capacity, expiratory reserve volume and vital capacity markedly reduced.	Pulmonary schistosomiasis; chronic cor pulmonale; pulmonary function studies all normal but for maximum breathing capacity This may be related to stiffness of lung under a timed maximal effort. One week later patient became cyanotic. Pulmonary vascular disease without pulmonary parenchyma disease.	

dyspnea, due entirely to the pulmonary disease, is very commonly encountered. The presence of this symptom, then, does not necessarily imply cardiac failure as it so often does in other forms of heart disease. Cyanosis, likewise, may be due entirely to the pathologic condition in the lung, though it is frequently aggravated when cardiac failure occurs.

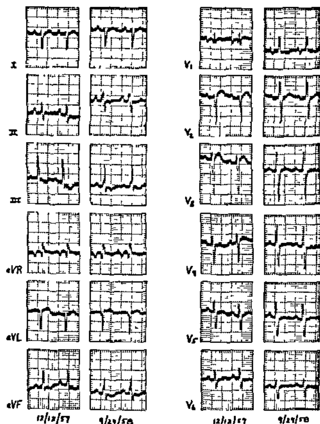


Figure 5 Patient I M with Hamman-Rich syndrome listed in Table I The findings are classical for right ventricular hypertrophy with considerable increase in the abnormality over a nine-month period

As a result of the development of pulmonary function studies it has become possible in recent years to estimate with a fair degree of accuracy the degree and type of pulmonary insufficiency in any given case, and to follow the progress of the functional impairment with the advance of the pulmonary disease. The findings in three patients with serious pulmonary disease are presented in Table I, and will serve as an illustration of the value of these tests. It will be noted that in the first patient (J. B.) the pulmonary function studies indicate severe obstructive pulmonary disease with inability to ventilate the lungs properly, resulting in arterial oxygen unsaturation. This is consistent with the clinical diagnosis of pulmonary emphysema. In the second patient the pulmonary function studies were compatible to those in patients with severe restrictive pul-

monary disease and the clinical diagnosis of Hamman-Rich syndrome. The major abnormality was a markedly reduced vital capacity. The electrocardiogram (Figure 5) demonstrates the progressive development of right ventricular hypertrophy. Case three (J. R.) illustrates essentially normal pulmonary function studies in the presence of severe dyspnea and right-sided heart failure. The electrocardiogram and chest x-rays were those classically associated with pulmonary artery hypertension. Two days prior to death, severe cyanosis appeared which was not amenable to correction with oxygen. The clinical and autopsy diagnoses were pulmonary schistosomiasis with diffuse pulmonary arteriolitis. The decreased maximum breathing capacity perhaps represented a degree of lung stiffness which interfered only with a maximum ventilatory effort. No pulmonary parenchymal disease was present.

Three stages may be recognized in the development of the pulmonary heart disease syndrome. The first is that during which pulmonary hypertension is developing but maintenance of pulmonary circulation exists. In the case of obstructive emphysema this may last ten to fifteen years with gradual elevation of pulmonary pressure corresponding to the progression of impaired ventilation and hypoxia.[100] At this time there is seldom any evidence of cardiac involvement. There are no symptoms other than those which can be accounted for by the lung disease, and on physical examination accentuation of the pulmonary second sound, due to pulmonary hypertension, may be the only cardiac finding. Other findings gradually appear, marking the onset of the second stage with involvement of the heart and development of right ventricular hypertrophy. These include a forceful subxiphoid or left parasternal systolic thrust, a pulmonic systolic or left parasternal diastolic murmur, a split pulmonary second sound and palpable closure of pulmonary valves. Recently, Leatham[63] has described an early systolic sound resembling a widely split pulmonic first sound in patients with cor pulmonale and a dilated pulmonary artery. Unlike a split first sound, which is often best heard at the mitral or tricuspid area, this is heard most distinctly in the left second or third intercostal space next to the sternum. The roentgenographic and electrocardiographic abnormalities which have made possible a recognition of the disease process in this stage will be discussed later. Patients generally remain in this state of compensated heart disease a considerable period of time, often years, before gradually passing into the third stage, that of congestive heart failure. Those with alveolocapillary block, however, generally have a much shorter life span after the onset of their pulmonary disability.

In the third stage, the well-known manifestations of decompensation of the right ventricle appear. These include: increased venous pressure, enlargement of the liver, edema of the dependent parts, albuminuria, and other evidence of renal congestion in the urine, and, in advanced cases, ascites and hydrothorax. Enlargement of the heart may be detected on physical examination although this is often very difficult in the presence of emphysema or other advanced pulmonary disease. Gallop rhythm may be heard along the left sternal border. Its presence indicates a poor prog-

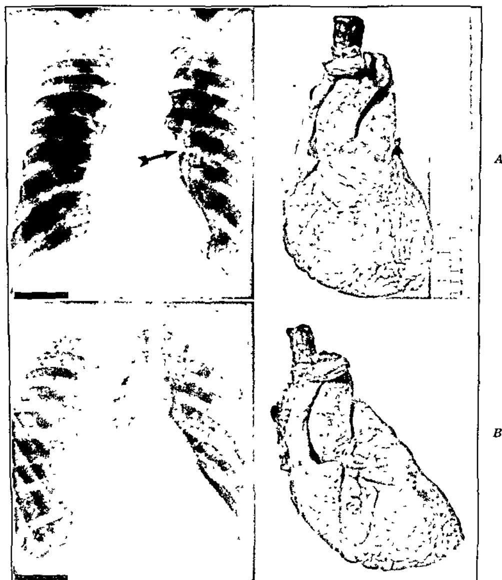


FIGURE 6 A, Pulmonary emphysema with chronic pulmonary heart disease in a male, aged sixty-six Dyspnea and productive cough for five years Congestive *failure for two weeks prior to first admission to hospital Marked improvement*

nosis. Major arrhythmias in general have been unusual in chronic cor pulmonale. In 1958, however, Corazza[22] reported various arrhythmias in forty-seven of 122 such patients (31 per cent). Most of these arrhythmias were premature atrial and ventricular beats and supraventricular tachycardias. In patients who have reached an advanced stage of failure, the course is often a progressive one despite intensive treatment.

Roentgenologic Examination: This is of paramount importance in the diagnosis of pulmonary heart disease. In the first place, this study will yield important information concerning the character of the pulmonary disease present. In the second place, a careful examination of the heart contour will usually give evidence of cardiac involvement, when such is present, by demonstration of enlargement of the outflow tract of the right ventricle.[3,67] The latter is an important early indication that pulmonary hypertension exists, and may be recognized when the normal concavity of the left border of the cardiac silhouette is replaced by a bulging convexity representing enlargement of the pulmonary artery and conus (Figures 3 and 6). This bulging convexity is usually more marked in the right anterior oblique position than in the anteroposterior. When there is uncertainty as to the status of the right ventricular outflow tract in the conventional roentgen examination, accurate measurement of the individual chambers of the heart and of the thoracic vessels may be achieved by angiocardiography. This method consists in the rapid intravenous injection of 70 per cent Diodrast or 90 per cent Hypaque, followed by the taking of roentgenograms at short intervals to visualize the passage of the dye through cardiac chambers and thoracic blood vessels. This method has greatly extended the value of roentgenology in the diagnosis of early chronic pulmonary heart disease.

In the later stages of chronic pulmonary heart disease, enlargement of the body of the right ventricle is added to the earlier outflow tract enlargement, and there will be noted at this time a prominence of the right ventricular contour in the left anterior oblique position. Enlargement of the right atrium is seen infrequently. There is usually no increase in the transverse diameter of the heart, a fact worthy of considerable emphasis since this measurement is so often relied upon as an index of cardiac size. Characteristically, enlargement of the hilar shadows, reflecting the enlarged main and stem pulmonary arteries, is present. There is then, however, an abrupt reduction in caliber of secondary and tertiary branches resulting in oligemic peripheral lung fields.[51,94] This abrupt transition may be well demonstrated by angiocardiography.

Mitral stenosis and certain forms of congenital heart disease (notably pulmonary stenosis and patent ductus arteriosus) are important causes of enlargement of the right ventricular outflow tract, and must, therefore, be differentiated from pulmonary heart disease. In mitral stenosis there will be evidence of left atrial enlargement demonstrable in the left projection with a barium-filled esophagus. Left atrial enlargement is only rarely observed in pulmonary heart disease. Congenital abnormalities may be differentiated usually by the history and physical findings, but cardiac catheterization and angiocardiography may be necessary in some cases.

A sign frequently observed fluoroscopically in cases of advanced pulmonary emphysema or fibrosis is inspiratory distention, followed by expiratory diminution of the cardiac silhouette, more marked on the right side than on the left.[102] This sign is a manifestation of marked diminution in lung tissue elasticity. When lung function is so impaired, the pulmonary tissue cannot rapidly adjust itself to changes in the volume of the thorax. The respiratory movements of the chest wall are thus transmitted to the heart. Whether or not this effect plays any significant role in the eventual development of heart failure is not known.

Electrocardiogram: This may or may not prove of diagnostic value in patients suspected of having chronic pulmonary heart disease. When definite right axis deviation is present and is not accounted for by the presence of mitral stenosis or congenital heart disease, it is of considerable value. In many cases of chronic cor pulmonale, however, a normal axis or even left axis deviation may be found. This is particularly true in cases of emphysema with coexisting hypertension of the greater circulation.

Abnormalities of the P wave are found in some cases, and, when present, are of diagnostic importance. These changes consist in increased height and breadth of the P waves in Leads II and III. Notching is rarely seen. During periods of congestive failure the enlargement of these waves may disappear, reappearing with return of compensation (Figure 2). Moreover, variability in size and shape and direction of the P wave may occur, as seen in emphysema particularly, without apparent change in the clinical course.[82] The P-wave enlargement so commonly seen in cases of mitral stenosis is usually most marked in Leads I and II, and conspicuous notching is frequently present. In congenital pulmonary stenosis, increased height of the P waves is not associated with increased width.

The application of unipolar electrocardiography to the problem of the chronic cor pulmonale[89,127] has been extremely helpful. It has been shown that the typical findings in the standard leads are due to a rotation of the heart in a clockwise manner on its longitudinal axis with a backward displacement of the apex. In the precordial leads there tends to be a reversal in the ratio of the amplitudes of the R and S waves in Leads V_1 and V_6 characterized by an abnormally large R wave in proportion to the S wave in Lead V_1, and a prominent S wave in Lead V_6. Johnson[65] and Scott[108] have shown that when there is electrocardiographic evidence of right ventricular hypertrophy there will be mean pulmonary artery hypertension of 30 mm. Hg or more. Dexter has found in addition that the right ventricular hypertrophy pattern did not appear until total pulmonary resistance exceeded 750 dynes per second per centimeter^{-5}.[31] Completely normal tracings, however, may be obtained in patients with well-advanced pulmonary heart disease. Occasionally, incomplete or complete right bundle branch block is found in place of the right ventricular hypertrophy pattern. The T waves from the right precordial leads are frequently inverted, while those from the left precordium are generally upright. If there is associated disease which causes left ventricular strain (e.g., hypertension in the greater circulation) there may be an absence or diminution in the amplitude of the S waves from the left of the precordium A QS type of complex

in the right precordial leads in chronic cor pulmonale occurs with considerable frequency and does not indicate the presence of myocardial infarction.

Studies of the Circulatory Function: Various tests of circulatory function are of diagnostic value in many cases of pulmonary disease. Oppenheimer and Hitzig have extensively investigated this subject.[93] They have shown that in uncomplicated pulmonary disease the findings in these tests are normal. This is also true even in the early stages of pulmonary heart disease when right ventricular enlargement is present, but in which decompensation has not occurred. *The presence of abnormal circulatory measurements indicates that pulmonary insufficiency is complicated by myocardial insufficiency.* The myocardial failure may be incipient or frank isolated failure of the right side of the heart resulting from the pulmonary disease, or it may be due to unrelated, coexisting cardiovascular disorders which produce either left ventricular or universal heart failure. Incipient right-sided heart failure is characterized by the presence of a normal initial venous pressure and a varying rise in this pressure during compression of the right upper quadrant of the abdomen. The arm-to-lung circulation time (ether time) may or may not be prolonged, and the lung-to-tongue time (saccharin or Decholin time minus ether time) is normal. In frank isolated right-sided failure there is a high initial venous pressure, a considerable rise in pressure on right upper quadrant compression, a prolonged arm-to-lung time, and a relatively normal lung-to-tongue time. Left-sided heart failure (due to coexisting cardiovascular disease, such as hypertension or coronary artery disease) is characterized by a normal initial venous pressure, with or without a rise on right upper quadrant pressure, and a considerably prolonged lung-to-tongue time. Universal heart failure, secondary to disease of the left side of the heart, and possibly to pulmonary disease in addition, combines these features of left- and right-sided heart failure.

Special mention should be made of the usefulness of cardiac catheterization Obviously this will reveal pulmonary artery hypertension if it is present. The presence of a normal pulmonary capillary pressure aids in the differential diagnosis by ruling out processes in the left side of the heart as a cause of the pulmonary hypertension. The wedge pressure is normal in instances of pulmonary disease.[19,100] Care must be used in the selection of patients for catheterization as sudden death has been reported during or shortly after the procedure in those having primary pulmonary hypertension.[105]

Diagnosis: The following criteria should be established before making a diagnosis of chronic pulmonary heart disease: (1) the presence of pulmonary disease of a type which may be responsible for hypertension of the lesser circulation; and (2) evidence by roentgenogram or electrocardiogram of right-sided heart hypertrophy, not explained by the presence of mitral valve disease or congenital cardiac abnormality or left ventricular insufficiency. Right ventricular failure in a patient presenting these qualifications is further evidence in favor of such a diagnosis, but need not be present. Circulatory measurements may indicate incipient right-sided heart failure in the absence of other findings usually relied upon for a diagnosis of myocardial insufficiency. These measurements and those of

cardiac catheterization may also aid in differentiating cases of pulmonary heart disease and those of pulmonary disease in which there is a coexisting cardiac condition of a type unrelated to the pathologic condition in the lung.

Treatment: Since the cardiocirculatory complications arise from the underlying disturbance in pulmonary function, the treatment of chronic cor pulmonale must include an attack upon the pulmonary insufficiency. Treatment of the latter can only be beneficial if the nature of the lung disease be known. The first step in treatment is proper diagnosis of the underlying pulmonary disease.[55]

It is not within the scope of this chapter to discuss in detail the treatment of the various etiologic factors previously described. The reader is referred to several excellent reviews on this subject.[28,43,54,59,94] Brief emphasis may be placed, however, upon the more general and practical aspects of such treatment since thoughtful attention at strategic times during the course of the primary disease may prevent the development of right-sided heart failure.

From the section on etiology it is evident that the treatment of chronic cor pulmonale usually involves the management of chronic obstructive emphysema or pulmonary fibrosis. In review, three fundamental disturbances in pulmonary function develop in the former: (1) gross impedance of air flow in and out of the lungs, (2) the air is unevenly distributed to the alveoli, and (3) the blood passing through the lungs is similarly unevenly distributed to the alveoli. The last named is not amenable to therapy, but the first two are. The impedance to air flow and the uneven distribution of alveolar gases stem from loss of elasticity of lung tissue, bronchiolar spasm, mucosal edema, retention of secretions and exudates. Diligent application of *vaporized bronchodilators (Isuprel, Vaponefrin), antibiotics, sputum* liquefiers (potassium iodide, terpin hydrate), oral bronchodilators (sublingual Isuprel tablets, aminophylline, ephedrine), postural drainage, bronchoscopy, aerosol mists (trypsin), synthetic detergents (Alevaire), and occasionally adrenal steroids[11] for refractory bronchospasm will maintain pulmonary sufficiency for years. Education in abdominal breathing exercises may increase diaphragmatic excursions remarkably. Acute infections must be scrupulously avoided or treated since it is during such episodes that anoxia and hypercapnia may become the dominant feature. In such patients, hospitalization is required with prompt administration of the above procedures as required. The use of sedatives is to be stringently avoided because of their tendency to produce respiratory depression. Oxygen, if used in the presence of elevated serum carbon dioxide, must be given intermittently or in conjunction with a mechanical respirator to avoid complete suppression of the respiratory center and apnea. Diamox has been found useful occasionally in lowering serum bicarbonate and serum pH, thereby reducing the depressant action of elevated plasma carbon dioxide on the respiratory center.[107,116,117]

In the presence of pulmonary fibrosis and pulmonary vascular disease, the anatomic lesion is chiefly responsible for the pulmonary hypertension rather than the anoxia and hypercapnia seen with emphysema. The out-

look, therefore, is bleak at best. Rigorous restriction of physical activity is of primary importance in an attempt to reduce exacerbations of pulmonary hypertension. The use of cortisone and its derivatives has offered some hope of limiting the cellular proliferation in some cases of alveolar-capillary block.[120] The previous admonitions regarding pulmonary infection are, of course, applicable in the avoidance of anoxia and carbon dioxide retention. Smoking is absolutely contraindicated because of its irritating and bronchoconstricting effects.

The specific cardiac therapy of patients in failure with chronic cor pulmonale consists in the judicious use of those measures universally employed in heart failure due to other forms of heart disease.[59] These include rest, digitalis, diuretics, and low-salt diet. Digitalis was once considered valueless in chronic cor pulmonale.[63] Cournand, however, has convincingly demonstrated that digitalization ultimately results in a decreased cardiac output, decreased pulmonary artery pressure, and improved pulmonary function.[39] The last is evidenced by improved arterial oxygen saturation Cardiac rate alone must not be used as the sole guide to full digitalization since these patients, even when not in failure, tend to run resting ventricular rates of 90 to 100. Digitalis, if pushed, may easily produce intoxication. The effects of digitalis are not as dramatic as those often seen in left ventricular failure. Diuretics are indicated when frank right-sided failure has occurred.

Special mention should be made of the value of oxygen administration, a method of treatment emphasized by Barach.[5] Patients with pulmonary insufficiency of sufficient severity to produce cardiac embarrassment show either a diminished oxygen saturation of arterial blood or normal oxygen levels maintained at the expense of increased ventilation. Continuous administration of oxygen to these patients often relieves dyspnea and reduced pulmonary ventilation. As noted previously, however, great care must be exercised when it is administered in the presence of respiratory acidosis, and it may be necessary to use intermittent or mechanical respirator.

Phlebotomies of 300 to 500 milliliters at a time may be dramatically effectual in patients with severe anoxia plus polycythemia and hypervolemia. Serial determinations of hematocrit readings and hemoglobin values will permit reduction of hematocrit levels to 45 to 50 per cent without reduction of hemoglobin below 12.0 grams.

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HUGO ROESLER, M.D.
AND
JACOB ZATUCHNI, M.D.

15

Cardiac Hypertrophy and Dilatation

Introduction: Hypertrophy and dilatation of the heart are commonly present in primary diseases of the cardiovascular system. They also occur in systemic diseases, many of which are known and understood moderately well, while others that are undoubtedly a factor in their causation, have not yet been discovered. On the other hand, it should be emphasized that the presence of a heart of normal size and shape does not exclude heart disease.

Methods for estimating the size of the heart during life are necessarily indirect and depend principally upon muscle mass, force of contraction and blood content. Since the size of the normal heart has a wide range of variation, a considerable increase must occur before enlargement is appreciated clinically or radiologically.[1,2]

The use of "enlargement" is preferable to that of "hypertrophy" or "dilatation" because the determination of these components of enlargement is very uncertain. Moreover, an element of both is almost always present. The recognition of dilatation during life is usually retrospective and presumptive.[3] Although the volume of residual blood in the right ventricular cavity may be determined approximately by special technics,[4] it has only a crude correlation with the total capacity of the heart. Angiocardiography is useful in determining intracardiac volume and thickness of heart wall.[5]

The lay individual is fearful of the diagnosis of enlargement as an indication of an incurable condition, leading sooner or later to death. The practitioner is likely to diagnose enlargement as a disease, *per se*. Of course, it is not the enlargement which is injurious, but that which is responsible for the enlargement. A full understanding of cardiac enlargement, of its functional and prognostic evaluation, and of its proper treatment demands knowledge of the conditions that produce it and of the rate at which they act.[6]

Anatomy and Pathology: The size of the heart at autopsy is usually determined by measuring various diameters, the thickness of the myocardium and by weighing Important factors which must be considered in an analysis of heart weight are body weight and length, sex, and nourishment. Tables are available in which these are correlated in normal individuals.[7,8,9]

The heart weighs approximately 300 grams in the normal adult male and approximately 250 grams in the normal adult female.[9] Some prefer to relate the weights of the body and the heart, feeling that the whole must be related to any of its parts. At birth, the heart weight averages 0.62 per cent of the body weight in males and 0.45 per cent in females.[7] In adults, it is approximately 0.55 per cent in males and 0.53 per cent in females.[10] Smaller percentages, such as 0.43 per cent in males and 0.40 per cent in females, have been reported,[7] but it has been suggested that these may be too low, inasmuch as the data were obtained from individuals with emaciating diseases and body weight at death was not considered.[11] Greenwood and Brown[12] found that the weight of the heart is approximately 0.575 per cent of the weight of the body. Zeek[8] preferred correlation of heart weight with body length rather than body weight, because height is a much more stable factor in body build and is much less influenced by disease In the normal male, the heart weight, in grams, is 1.9 body length (in centimeters) $-$ 2.1 $\pm$ 40, and in females, 1.78 body length $-$ 21.58 $\pm$ 30. Various diameters of the heart at autopsy may be measured, such as the distance from the base to the apex or from one border to another.[13] These are necessarily crude and the range of normal variation is considerable. For the recognition of hypertrophy, the thickness of the myocardium is measured. Such measurements should not include the other linings of the heart, or the papillary muscles or the columnae carneae. The thickness of the myocardium of the outer wall of the left ventricle midway between the apex and the mitral valve is 10 to 12 millimeters, and that of the right ventricle midway between the apex and the tricuspid valve is 3 to 4 millimeters.[14] The actual measurement should be accompanied by a statement describing the gross and microscopic appearance of the myocardium

Hypertrophy refers to an inherent enlargement of the muscle fiber and not to an increase in size due to edema, fibrosis, fat, amyloid, or glycogen. The myocardium of the hypertrophied heart is usually firm, beefy and thickened. The papillary muscles and the columnae carneae are prominent. The endocardium may be opaque. There is an increase in size of the muscle fibers, both in transverse and long diameters. The nuclei are enlarged and may be distorted and hyperchromatic. The normal ratio of one capillary per muscle fiber is preserved. There may be inflammatory and degenerative changes, or fibrosis that may or may not be related to the hypertrophy.

Dilatation denotes an enlarged capacity of the cardiac chambers A dilated heart is usually flabby in consistency. The valve orifices may be widened and the intracavitary muscle bundles flattened. The intercalated disks of the muscle fibers particularly those near the endocardium may be increased. Various types of degenerative changes depending upon the underlying cause may be observed.

More objective methods for the diagnosis of dilatation are desirable. The capacity of the heart has been measured by filling the heart with liquid under pressure or with melted wax. Another method consists of determining the volume of the myocardial mass by the principle of dis-

placement or by dividing the weight of the myocardial mass by the specific gravity of the myocardium that has been estimated to be 1.03. The capacity of the heart could then be derived from a consideration of the heart volume estimated from roentgenographic measurements and the myocardial volume.[3]

The term *tonogenous dilatation* refers to a compensatory dilatation of the healthy heart muscle because of an increased resistance to outflow of blood. It begins in the outflow tract of a ventricle which is below the aortic orifice in the left ventricle and in the pulmonary conus in the right ventricle and progresses against the direction of the blood stream down to the apex. Subsequently and slowly, the inflow tract is involved, again in a direction opposite to that of the blood flow so that the dilatation finally reaches the respective A-V rings. Elongation of the heart prevails over widening. *Myogenous dilatation* refers to dilatation closely associated with impaired contractility of the damaged myocardium. It involves simultaneously all parts of the ventricle in question quite uniformly and the result is a predominance of widening over elongation.

The Nature of Cardiac Enlargement: Why the heart enlarges is unknown. A stimulus for enlargement is frequently a demand for an increased cardiac output or an obstruction to blood flow either within the heart or in the peripheral circulation. Under such circumstances, it is believed by some that the heart enlarges because more work is required. Others believe that enlargement is a consequence of a diminished blood supply or of tissue injury. Most investigators believe that it is related to a stretching of the muscle fibers resulting in a larger surface area for greater nutritive diffusion.[3] Any muscle will increase in size if perfused with more blood. But, the ratio of one capillary per muscle fiber does not change with increased size of the fiber. Moreover, since the basis of this theory rests upon Starling's law of the heart, it is pertinent to be reminded that the validity of this law depends upon equal degrees of myocardial responsiveness[15] Hypertrophied hearts are uniform only in the sense of being enlarged hearts but not in the degree of enlargement, cardiac output, work capacity, or efficiency

Our preoccupation with heart failure and the knowledge of its almost universal association with increased heart size has resulted in undue emphasis of mechanical factors alone. Catheterization studies have demonstrated that cardiac enlargement may exist without change in cardiohemodynamics.[16] Moreover, experimental and clinical cardiac hypertrophy due to such non-mechanical factors as infection, avitaminoses and endocrinopathy and others are well known.[17,18] There is, therefore, an increasing tendency to consider primarily the metabolism of the heart and, in the future, the influence of mechanical factors will have to be interpreted upon the basis of biochemical changes including energy production and utilization.[19]

The enlarged heart is not necessarily a poorly functioning heart. Most individuals with increased heart size have normal effort tolerance. It is well known that individuals with valvular disease, such as aortic regurgitation, may experience steadily increasing heart size without symptoms

or limitations. Usually, it is the physician who imposes the limitations. Whether or not these restrictions are beneficial in the absence of heart failure is not established. They are based upon the assumption that there is a limit to cardiac hypertrophy and that any increase beyond this limit will result in cardiac decompensation. This hypothesis presupposes the existence of not only an absolute limit of hypertrophy but also that hypertrophy alone is present. It has been stated that hypertrophy is at a maximum when all of the muscle fibers are enlarged and uniform in size. *Recent studies, however, suggest that even in the largest hearts, no such* uniformity exists and that even if the single muscle fiber has reached a maximum limit, daughter fibers arise and subsequently increase in size.[14] The heart is structurally and chemically prepared for marked increases in size.

Enlargement of the heart does not mean hypertrophy alone. There is probably always an associated dilatation. It has been suggested that dilatation is dominant early in those with valvular defects, and hypertrophy in those with hypertensive or coronary artery disease.[3]

Enlargement of the heart is, of course, reversible. However, when the heart decreases in size after it has been enlarged, the assumption is that dilatation or pseudohypertrophy due to edema or other causes was present and not true hypertrophy. A priori, it is felt that true cardiac hypertrophy is irreversible. Experimentally, however, there is *evidence* that suggests the reversibility of cardiac hypertrophy.[20] Furthermore, it can be cited that skeletal muscle appears to decrease in size after abstinence from exercise and it is not clear why cardiac muscle should re*spond differently. If the heart enlarges in size and remains* enlarged in spite of removal of known causative factors, one can assume the presence of underlying myocardial disease, either pre-existing and unrecognized or consequent to the enlargement.

It is almost needless to point out that two or more etiologic factors may be responsible for *cardiac enlargement*. To cite only a few examples: In eighty per cent of the patients with coronary thrombosis and cardiac enlargement, other diseases, such as hypertension and heart failure, may account for the enlargement. Similarly, thyrotoxicosis or anemia may be associated with cardiac enlargement but other diseases affecting *the heart* are usually present.[1]

Enlargement may affect the chambers of the heart unequally. In respect to the left ventricle the following conditions may be mentioned: *Hypertension (of any etiology, including acute and chronic* glomerulonephritis, and coarctation of the aorta); aortic regurgitation, mitral regurgitation, aortic stenosis, coronary artery sclerosis, aneurysm of the wall. The right ventricle is involved predominantly in the presence of mitral stenosis; in the late stages of congestive failure from almost any cause; occasionally in the presence of systemic hypertension without *failure*; chronic disease of the pulmonary parenchyma, such as emphysema; obstructive disease in the lesser circulation (sclerosis, endarteritis, chronic embolization); tricuspid regurgitation; interatrial septal defect; pulmonic regurgitation *or stenosis; B-avitaminosis. The left atrium* is particularly

enlarged in the presence of mitral valvular disease; and this especially the case when the disease results from fibrosis of the wall following rheumatic myocarditis, but is also observed with failure of the left ventricle; while for the right atrium mention should be made of right ventricular failure, tricuspid regurgitation or stenosis, and interatrial septal defect. It should be stated that the degree of enlargement in the presence of valvular lesions does not always seem to be closely correlated with the apparent extra load.[21]

The principal direction of expansion of the different heart cavities is as follows: Left ventricle dorsad and to the left, but also to the right and ventrad; right ventricle to the left and ventrad, but also dorsad; left atrium dorsad; right atrium to the right and ventrad.

The more generalized form of enlargement is noted with a number of conditions, some common and some rare, *viz.*, combined valvular lesions; advanced stages of congestive failure of different etiology; myocardial lesions in the course of rheumatic fever, diphtheria, grippe, and typhoid; *Fiedler's type of myocarditis, acromegaly; and severe and prolonged* anemia.[22] In this connection it is proper to state that all myocardial lesions of toxic-infectious, endocrine, or nutritive origin may lead, but not necessarily, to cardiac enlargement. Among other causes may be mentioned arteriovenous fistula; marked bradycardia; glycogen storage disease; rhabdomyomatosis; hemochromatosis with infantilism, transposition of the great arterial vessels; common arterial trunk; origin of one or both coronary arteries from the pulmonary artery; bilocular and trilocular heart.[23]

Prolonged and strenuous physical activity carried on as endurance tests (skiing, rowing, cycling, long distance swimming, and running) may, but need not, bring about a slight degree of enlargement which should be looked upon as a physiological process of adaptation.[2,24,25]

Enlargement of a few special types is reversible and this will be mentioned under TREATMENT.

Although a rapid change in heart size is more likely to be seen in the young than in the old, it is related more to the nature of the underlying *disease rather than the age of the individual. Clinically recognizable en*largement may occur one week after the onset of acute rheumatic fever or acute glomerulonephritis. Hypertrophy requires at least three to six weeks for its development and this will take place in a case with rheumatic infection and developing valvular lesion in spite of complete bed rest.

The rate and degree of development of enlargement depends primarily upon the severity and localization of the disease. The more marked, for instance, the toxic damage, the greater will be the cardiac enlargement. A second factor which contributes to cardiac enlargement is physical overexertion while the process is still active Enlargement, as a rule, is not steadily progressive. It is likely to remain fixed in its degree for months and years.[21]

Acute dilatation of the heart is undoubtedly a rare condition. Severe toxic damage such as noted in the presence of diphtheritic infection is per-

haps the best instance. The right heart may dilate subsequent to pulmonary embolism. Contrary to common belief, general enlargement does not follow subsequent to an attack of coronary thrombosis. This remark does not apply to the development of an aneurysm which takes the form either of a localized bulge or, if located in the apical portion, simply



FIGURE 1 Orthodiagrams of a normal heart, as drawn in the anterior and left lateral views (reduced to one-fourth actual size). The three main diameters are indicated by solid lines Anterior view: The oblique diameter —L— connects the cardiovascular junction at the right with the farthermost point at the left lower pole The broad diameter —B— represents the sum of the lengths of two perpendiculars dropped to the line of the oblique diameter Lateral view: The depth diameter—$T_{D\,tr}$—is the sum of lengths of two perpendiculars dropped to a line which connects the region of the bifurcation of the trachea with the sternodiaphragmatic angle As average figures for a male, L 13 6 cm , B 10 cm , $T_{D\,tr}$—9 3 cm have been chosen.

The volumetric cardiac value is obtained by forming a product of these three figures times a constant 0 45 (formula of Benedetti and Bollini). The value thus obtained approaches the actual volume of the heart (as expressed in cc) In this instance it is 569 This formula has been checked by actual volumetric reconstruction and submersion of the model in water The error for normal hearts was shown to be between −8 per cent and +8 per cent and for diseased hearts between −10 per cent and +15 per cent

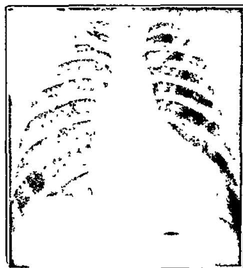
causes an elongation of the heart. This may occur within a week following the infarct.

A healthy heart may dilate suddenly. This is clearly noted in fluoroscopy during the pause following a premature ventricular beat; likewise, when the breath is held, the glottis closed, and a strong effort is made to inspire. Strenuous exertion never causes abnormal dilatation of a healthy heart. Paroxysmal rapid heart action may be followed by dilatation, but only in connection with the development of congestive failure. Care should be taken not to confuse acute dilatation of the heart with collection of fluid in the pericardial cavity. Another diagnostic error occurs in thinking of an acute dilatation when actually vasomotor collapse is present.

Symptoms: There are no symptoms of cardiac enlargement. Although palpitations or forceful beating of the chest wall may be experienced, these symptoms are more frequently present in those without heart disease. The development of symptoms depends upon associated disturbances and the functional capacity of the enlarged heart.

Diagnosis: Enlargement of the heart in the living is studied in both its static and dynamic features by x-rays and by inspection and palpation of the chest wall. Percussion is to be carried out but should be controlled by radiological methods whenever possible. The electrocardiographic study is of limited value for the diagnosis of enlargement *per se*, but is very useful for complicating features.

Radiology: *Fluoroscopy* is the method of choice. A good dark adaptation of the retina is a prerequisite. The oblique views must be studied in



addition to the anterior view The screen image, as obtained by fluoroscopy, represents, of course, a considerable magnification of the object size. This is overcome by taking an orthodiagraphic tracing. The film image as obtained by a teleroentgenogram at a distance of six feet shows a magnification of nearly ten per cent. The absolute heart size is best determined by a computation formula.

Using the metric system, a product is formed from the oblique and broad diameter (anterior view) and oblique depth diameter (lateral view) and this is multiplied by 0 45. The value thus obtained expresses approximately the heart volume in cubic centimeters The medium value for healthy males is 569 2 and for the healthy female 422 6, with a standard deviation of 85 4 and 64 1 respectively. A simple and practical procedure is to rotate the sheet on which the orthodiagraphic silhouette is drawn by approximately 180° so that the base of the heart is pointing down, and place the patient's clenched right fist over the silhouette. These outlines will nearly coincide under normal conditions. It should be realized that the correlation coefficient between the size of the silhouette

and external measurements (weight, transverse diameter of the chest, etc.) is too low to have great statistical significance Standards for the various diameters of the cardiac silhouette that has been obtained by either orthodiagraphy or teleroentgenography and based upon height and weight are available. These values are to be used with the reservation that they are neither rigid nor absolute, for although a heart is probably enlarged if the diameters deviate more than fifteen per cent from the predicted values, approximately three per cent of normals may fall into this category. If measurement is attempted for the anterior view only, the frontal plane area, determined by either planigraphy or the product of the long and broad diameters and a constant (0.735) offers the least variation and is the preferred method for measuring "cardiac" size. It should be correlated with the transverse diameter of the thorax and the deviation of this value from the normal should be estimated. But, again, there is an appreciable overlap with the abnormal and a definite conclusion as to the presence of slight or moderate enlargement of the heart based upon this determination may be unwarranted Of course, the larger the heart, the more reliable the measurements in detecting cardiac enlargement. But, with larger hearts, clinical accuracy is also increased and the need for elaborate studies may be unnecessary. The best field of usefulness of these cardiac measurements is in repeated studies of the same individual. Granted that these are made under comparable conditions, particularly in regard to respiratory and cardiac phases, the resulting information far exceeds that obtained by any other method.

In the anterior view an enlargement to the left and caudad, associated with a well preserved or lowered waistline of the left middle contour indicates left ventricular enlargement. Care should be taken not to include in delineation and measurement the shadow which is caused by the extrapericardial, subpleural fat pad. The waistline will, however, be straightened out if a secondary right ventricular enlargement sets in. An enlargement to the left and craniad leading to a prominence of the so-called pulmonary segment may be seen in enlargement of the pulmonary artery, left atrium or its appendage and right ventricle. An enlargement to the right should be attributed as a rule, to the right atrium, and only exceptionally to the right ventricle. Occasionally an aneurysmal distention of the left atrium accounts for it. In the right anterior oblique view, a convex bulge in front should be attributed to the pulmonary artery or to the right ventricle and in this view the conus enlargement is particularly well noted. Dorsally, the mediastinum may be encroached upon by the left atrium and visualization of the barium-filled esophagus gives valuable information. In the left anterior oblique view, the right ventricle is seen to expand ventrad, the left ventricle dorsad and caudad, the left atrium dorsad and craniad. In the latter case, the left bronchus is displaced and sometimes considerably narrowed.

The commonest cause of right ventricular hypertrophy is left ventricular hypertrophy.[26] The roentgenologic diagnosis of hypertrophy of either ventricle in the presence of hypertrophy of the other is very difficult and frequently impossible. Usually, the clinical problem is clear and only roentgenographic confirmation of an enlarged heart with left ventricular preponderance is desired. But, in this era of cardiac surgery, our diagnosis must be more definitive. For instance, at present, the demonstration of

significant left ventricular enlargement in an individual with mitral stenosis contraindicates mitral commissurotomy. Unfortunately, the radiologist does not have any satisfactory criteria, as yet, for distinguishing left ventricular enlargement in the presence of marked right ventricular enlargement. Caudad displacement of the apex in the anterior view and increased curvature of convexity posteriorly in the left anterior oblique view may be helpful in recognizing left ventricular enlargement. Radio-



FIGURE 3 Female, age eighteen Chronic nephritis following scarlet fever five years ago B P. 180/110 Anemia (R B C. 1 46 mill, Hb. 35 per cent) Roentgenogram, anterior view· The silhouette is markedly enlarged and of a globular shape A moderate degree of pulmonary congestion is present. Postmortem Hypertrophy and dilatation of the heart, weight 540 grams. Coronary arteries negative. Chronic glomerulonephritis

cardiography, a method for determining the cardiac circulation of injected radioactive substances, may offer a means for the differentiation of right and left ventricular enlargement.[27,28]

During fluoroscopy, one can observe unusual intracardiac or border pulsations.[29] The demonstration of valvular calcification suggests the presence of an obstructive valvular lesion as a cause for chamber enlargement. A systolic outward pulsation of the region of the left atrium and auricular appendage would suggest the presence of mitral insufficiency. Paradoxical or limited pulsations of the left ventricular border may confirm the presence of an underlying ventricular aneurysm or recent myocardial infarction.

With angiocardiography, detection becomes possible of shunts, obstructions and pericardial effusion. Also, myocardial hypertrophy may be suggested by increased widening of the area between the heart border and the injected dye or by bulging of the interventricular septum away from the affected side, and dilatation by visualization of chamber capacity.[5]

An understanding of the underlying pathology is enhanced by studying the size and shape of the aorta and of the pulmonary artery and its branches. The early recognition of left heart failure depends upon the roentgen demonstration of pulmonary congestion; also, *the shadow of the* azygos vein may be prominent.[30] Displacement of the heart may clinically be mistaken for enlargement and the radiological method reveals almost at one glance the presence and degree of causative factors such as pleural *effusion, pneumothorax, fibrotic shrinking or collapse of the lung,* abnormal position of the diaphragm, or chest deformity. Augmented heart action is another cause for overestimation of heart size by clinical means. Finally, radiology may assist in differentiating cardiac enlargement and pericardial effusion.

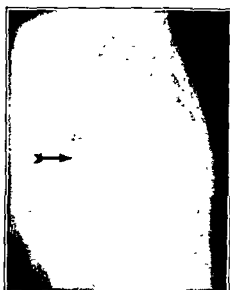
Percussion and Auscultation: With percussion, an attempt is made to determine roughly the portion of the chest wall that overlies the heart. It is a subjective, rather crude method which in the hands of the average physician yields inaccurate results. Since the right heart chambers are in close proximity to the ventral chest wall, one will obtain more reliable results so far as the right heart is concerned as compared with the left heart chambers. The bulk of the latter are dorsally located and hence poorly available to percussion. The commonest error encountered is *finding the left contour too far to the left and too far craniad.* Results are particularly poor in emphysematous and stout individuals. An attempt should be made to determine the position and shape of the left upper portion of the contour, the so-called "waistline of the heart." If this waistline is preserved, one will find only the *slightest degree* of dulness in the third left intercostal space. A marked degree of dulness indicates that the waistline has gone, *i. e.*, there is an enlargement of the pulmonary segment. Dulness may extend from 2 to 8 cm. towards the left of the left sternal border in the third intercostal space. An increased flatness on percussion over the lower third of the sternum, craniad to the upper border of liver dulness, indicates an enlargement of the inflow tract of the right ventricle. The latter finding is particularly noted in patients who have had failure in the past. A marked degree of flatness on percussion along the sternum, *starting as high as the level of the second intercostal space,* and associated with a marked extension of the cardiac dulness to the left, particularly in the third intercostal space, speaks in favor of a pericardial effusion. The left lower heart border should be percussed if the cardiac impulse is ill-defined or not available. Percussion of the right heart border and determination of the location of the trachea helps to decide as to whether or not the heart is displaced.

There are no auscultatory signs of cardiac enlargement. The intensity of heart sounds is not related to heart size but is dependent upon various other factors, mainly, atrio-ventricular conduction time, stroke output and intracardiac tension. An apical systolic murmur due to cardiac enlargement may be present. Usually, it is similar to the so-called innocent murmur, faint in intensity and blowing in quality, and, if due to the enlargement, should disappear or lessen in intensity with decrease in heart size. If the murmur is of greater intensity, or is harsh or musical, consideration should be given to the possibility of associated valvular defects.

Inspection and Palpation: Cardiac enlargement is manifested by a change in character or location of "cardiac" pulsations upon the chest wall. Clinically, the best indicator of heart size is the location of the apex impulse. Every effort should be made to ascertain its presence and location. Not infrequently, it is present only when the patient is erect, leaning forward and in



A



B

deep expiration. Occasionally, it may be present only in the recumbent position. A helpful guide is to locate its presence in the left lateral decubitus position and then to follow it medially as the patient rotates into the supine position. Occasionally, the apex impulse is missed because the physician examines only its anticipated location in the region of the left midclavicular line. The apex impulse is the most lateral and caudal point where a distinct thrust of the chest wall is felt.[31] With normal-sized hearts, the point of maximal impulse will coincide with the apex impulse, but with enlarged hearts, the point of maximal impulse may be 1 centimeter medial to the apex impulse. In normal adults, it is in the left fifth intercostal space. Rarely is it above or below this intercostal space. The respective intercostal space can be conveniently located by determining first the position of the junction of the manubrium and the body of the sternum, the so-called sternal angle or angle of Louis This prominence is on a level with the second rib. The second intercostal space is directly below the second rib. If the hand is now placed obliquely so that the fingers are in successive

be easily and properly numbered. Improper numbering of the intercostal spaces is a very frequent error. The apex impulse is 6.0 to 9.2 centimeters from the midsternal line with the patient in the erect position and slightly more in the recumbent position. It may vary from 5.0 to 14.0 centimeters from the midsternal line. The apex impulse will correspond to the ortho-



C.

FIGURE 4. C—Left anterior oblique view of case shown in Fig. 4. Note displacement and narrowing of left bronchus (arrow).

diagraphic apex of the heart in about forty per cent of cases. In the others, it will correspond to the left border of the heart or it will be 1 or 2 centimeters medial or lateral to the orthodiagraphic apex. In adults it is visible in not more than one-fifth of all cases, and it is rather uncommon to palpate it in the recumbent position of the middle aged or elderly person; if well-defined and at this age, the presence of hypertrophy should be suspected. Position and quality of the apical thrust may lead the examiner to erroneously assume the presence of some cardiac enlargement where there is none. Such an obtrusive apex beat slightly outside of the nipple line is noted particularly in children when there is some right-convex scoliosis of the spine; in boys during the rapid growth period of puberty; and in association with augmented heart action, as noted in the presence of thyrotoxicosis. The apical thrust may be neither felt nor seen in the obese and emphysematous, and is poorly palpable and shows a systolic retraction in the presence of mitral stenosis where hypertrophy and dilatation of the right ventricle push the left ventricle away from the ventral chest wall. Tricuspid regurgitation has the same effect. Only in exceptional instances of excessive enlargement of the right ventricle and of the right atrium, pushing the left ventricle to the left, such as is noted in instances of an interatrial septal defect, will a heaving apical thrust be observed as

a part of a diffuse systolic bulge of the precordium. The apical thrust is feeble or not palpable in the presence of dilatation without hypertrophy, with fluid in the pericardial or left pleural cavity, with edema of the chest wall, and is usually absent in constrictive-adhesive pericardial disease. Hypertrophy of the left ventricle causes a characteristic heaving resistant apical thrust. Dilatation superimposed on hypertrophy favors the development of a forceful apical thrust, because the left ventricle is then in closer contact with the chest wall. It is often noted that a fully compensated aortic stenosis or hypertension, with marked hypertrophy does not reveal the presence of an apical thrust until dilatation supervenes. A very broad apical thrust indicates a marked degree of dilatation (unless a narrow chest and thin chest wall are responsible for it). This in turn signifies the inability of the heart to completely discharge its contents Such a finding is, therefore, an unfavorable sign. The heaving and resistant quality of the apical thrust may be lost when failure sets in as expressed, for instance, by the appearance of gallop rhythm.

A careful study of the chest wall movement in heart diseases[32] gives valuable information as to the underlying dynamics: *Systolic Propulsion* (Quicker and More Marked Than the Diastolic Depression Which Follows)—A large systolic bulge of the wall chest which is most marked halfway between the left midclavicular line and the sternal border, palpable and often visible, is found predominantly in patients with advanced mitral stenosis. Here the right ventricle is enlarged, and during systole the depth diameter of the heart is increased, with the enlarged left atrium pressing the heart ventrad and thus furthering the development of the systolic bulge. Associated with this propulsion over the midportion of the chest is a flattening out of the lateral areas, for obviously if in a tense elastic system a deformity is set up in one area, it will affect the entire system.

A ventricular aneurysm arising as a rule from the left ventricle (usually following an anterior cardiac infarct) often gives rise to a cardiac thrust which is sometimes large and forceful in character. It is most commonly located at the level of the fifth left rib and, depending upon its seat, pulsations are situated lateral or medial to the midclavicular line and may approach the left sternal border. Pulsations caused by a ventricular aneurysm should be differentiated from those caused by right ventricular hypertrophy and dilatation in association with left atrial enlargement. The former is more circumscribed and further laterad; the latter is localized and more mediad and its extension is more lengthwise, *i. e*, along the sternum. The diagnosis of cardiac aneurysm is made more difficult in the presence of hypertension or mitral and aortic valvular lesions, for these conditions *per se* are responsible for a forceful cardiac thrust. Location of the pulsations in the fourth intercostal space, within the left midclavicular line, is definitely in favor of the aneurysmal origin of the pulsations. Furthermore, supporting evidence is obtained from the history and electrocardiographic findings indicating a preceding infarction. Conclusive evidence is given by observing the development of such a pulsation subsequent to cardiac infarction. A strong propulsion of the left chest wall to the left and ventrad is caused by forceful action of an enlarged left ventricle, while on

the right side there is commonly associated a simultaneous flattening of the ribs. Occasionally in the presence of aortic regurgitation or hypertension, there may be noticed a jerky systolic shift of the entire chest to the left.

A primary systolic propulsion on the right side of the chest wall with the maximum of pulsation, as a rule, found in the right midclavicular line between the fourth and sixth rib is noted in the presence of a high grade mitral regurgitation associated with an aneurysmal enlargement of the left atrium. The mechanism is one of impact of the blood regurgitating into the left atrium which, in turn, approaches the chest wall. A forceful systolic propulsion of the right caudal portion of the chest wall is noted in the presence of tricuspid regurgitation, where the back flow of blood suddenly enlarges the liver and this, in turn, is transmitted to the chest wall. In both foregoing conditions a jerky shift of the entire chest to the right may be noted.

Systolic Depression (Quicker and More Marked Than the Diastolic Propulsion Which Follows)—Such a depression is noted if the cardiac volume shows a sudden and abnormally great diminution during systole and when simultaneously an abnormally large amount of blood flows out of the thoracic cavity. This is exemplified by cases revealing a high degree of aortic regurgitation, although this is not a constant finding, because the systolic change in the shape of the heart acts as an opposing force, and in the presence of tricuspid regurgitation. The more rapidly this outflow of blood takes place from the thoracic cavity, the less will the inflow of air and venous blood be able to keep pace with and counteract the considerable fall in the systolic intrathoracic pressure. Likewise, the increase in the marginal excursions of the ventricle exerts an aspiratory effect on the chest wall The systolic depression is, of course, followed by a ventrally directed diastolic movement which is rather slow. If systolic depression exists, it will disappear when cardiac failure with congestion sets in; this is because of the diminution in the stroke volume.

Depressions are also noted if there is interference with the function of the pulmonary cushion, for it is obvious that the chest wall must follow the centripetal movement of the heart if the lung does not quickly take up this space left vacant by the heart and the chest wall. A rapid expansion of the lung parenchyma may be interfered with by pleural adhesion, by atelectasis which is not uncommon in the immediate vicinity of an enlarged heart, or because of a powerful apical thrust. Localized soft tissue depressions are thus observed mesiad to the apical thrust in left ventricular hypertrophy and dilatation, and laterad in right ventricular hypertrophy and dilatation.

Diastolic Propulsion (Quicker and More Marked Than the Accompanying Systolic Depression Which Either Precedes or Follows): This is noted in instances of chronic pericardial disease. In adhesive pericardial disease the following points are worthy of consideration: First, the inhibition of the systolic change in shape of the heart due to internal adhesions, interfering with the normal propulsive forces—particularly of the apical thrust; hence the effect of the systolic diminution

is altered by the presence of adhesions. The longitudinal shortening of the ventricular cone is interfered with and, therefore, a compensatory increase in the marginal movements of the heart results. Actually, such cases reveal during fluoroscopy a remarkably large amplitude. An aspiratory force on the chest wall, therefore, makes its appearance. Third, the aspiratory effect on the anterior chest wall is enhanced by the common association of pleural obliteration, which inhibits the lung parenchyma from acting as a buffer. Since the systolic change in the shape of the heart is interfered with, the centrifugal impulse due to the diastolic filling of the ventricles acts unrestrictedly on the chest wall. The resulting diastolic propulsion is directed mainly to the left and ventrad and is quite forceful, while the systolic depression is often less impressive. But exceptions occur. In the presence of an obliteration of the pericardial cavity with external fixations to the inner chest wall, providing the heart muscle functions well, ventricular systole deforms the left chest wall, which is followed by an elastic rebound during diastole. This forces the heart into a passive expansion and is associated with a reduplication of the second sound.

The second cause of diastolic propulsion is tricuspid regurgitation; here the right ventricle empties its blood not only into the lungs and liver, but also the influx of venous blood is counteracted. Hence, the diminution in volume leads to a systolic depression but the subsequent filling of the right heart causes a ventral and diastolic propulsion which is quicker and more abrupt than the preceding depression. It should be emphasized that the diastolic propulsion is often not recognized, and is erroneously ascribed to systolic action of the heart on the chest wall Such an error in timing should not occur, and is easily avoided by placing one hand over the chest and palpating the radial pulse with two fingers of the other hand.

Electrocardiographic Criteria for the Recognition of Cardiac Enlargement: Atrial enlargement is characterized by changes in the amplitude and direction of the P vector. In right atrial enlargement, the P vector rotates to the right of its usual position at sixty degrees, resulting in a small or iso-electric P wave in lead I and a large P wave in leads II and III. The P wave is sharply peaked and usually greater than 2.5 mm. in amplitude. The resulting pattern is sometimes referred to as the P-pulmonale pattern. It may be transient, as in acute heart failure, or permanent, as in atrial septal defects. Similar P wave changes, usually not of such amplitude, may be seen in normal individuals, particularly those with hearts of a vertical electrical position. In left atrial enlargement, the P vector is rotated to the left of its usual position, resulting in a smaller P wave in lead III and a larger P wave in lead I. The P wave is usually prolonged in duration, increased in amplitude and notched. Such a pattern is referred to as the P-mitrale pattern because it is present most frequently in those with mitral stenosis. Similar P waves may be seen in normal individuals or in those with heart disease other than mitral stenosis. Changes in repolarization may be manifested by a shift of the T_p segment in a direction opposite to the P wave. Usually, this shift of the T_p segment is masked by a super-imposition of the ventricular complex

Electrocardiographic manifestations of left ventricular enlargement include the following: (1) Increased amplitude of the QRS complexes, (2) delay in the intrinsicoid deflection of the QRS complex in leads facing the epicardial surface of the left ventricle, (3) deviation of the S-T segment in a direction opposite to that of the QRS complex, and (4) decreased volt-

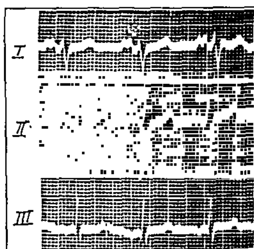
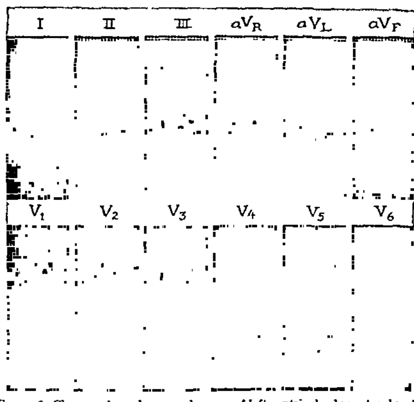


FIGURE 5 Female, age thirty-nine. Old rheumatic heart with mitral stenosis, considerable cardiac enlargement, and sinus rhythm which persisted up to death This took place two years later and was due to bronchopneumonia and pulmonary infarct (anatomic verification) Electrocardiogram reveals sinus rhythm, there is present widening and notching of the P-deflection in leads I and II, and a marked degree of right axis deviation is noted (initial deflection is down in lead I and up in lead III)

age of the T waves.[33,34,35] The S-T segment, if depressed, is convex upwards and the T wave, if inverted, has asymmetrical limbs. The most frequent abnormality is a depression of the S-T segment in leads V_4 to V_6. Increased voltage of the R wave may occur in less than fifty per cent of tracings. This percentage may be increased slightly if the sum of the voltage of the R wave in leads V_5 or V_6 and the S wave in lead V_1 is considered. There is frequently no delay in the intrinsicoid deflection that is measured from the onset of the QRS complex to the peak of the final R wave. The duration of the QRS complex may be prolonged to 0.12 second or longer, resulting in confusion with the diagnosis of left bundle branch block. On the other hand, left bundle branch block is associated frequently with cardiac enlargement. Indeed, some feel that the pattern of bundle branch block in the presence of left ventricular enlargement may be due, not to disturbance in the bundles but to delay in conduction throughout the hypertrophied ventricle and prefer to use the term "left ventricular retardation."[36] By means of vectorcardiography, left bundle branch block may be *distinguished from left ventricular hypertrophy.*[37]

The electrical position of the heart in left ventricular hypertrophy is usually semi-horizontal, rarely vertical. The QRS vector rotates leftwards, upwards and posteriorly. The time-honored reason given for this shift has been rotation of the heart around its long axis, so that the left ventricle

lies more posteriorly than usual. Recently, evidence challenging this concept has been advanced.[35] It has been suggested that the normal lie of the heart is unchanged in hypertrophied hearts and that the shift of the QRS vector occurs principally because of delay in depolarization of the epicar-



depressed, is convex upwards and the T wave is asymmetrical.

dial surface of the left ventricle. However, although the shift of the QRS vector is probably related to factors other than rotation of the heart, more evidence is necessary before accepting the idea of an unaltered position of the hypertrophied heart. Finally, it is to be emphasized that in at least twenty-five per cent of individuals with left ventricular hypertrophy, the electrocardiogram may be completely normal.

The electrocardiographic recognition of right ventricular hypertrophy depends primarily upon the presence in lead V_1 of an increased amplitude of the R wave with an intrinsicoid deflection of 0.03 to 0.05 second.[39] The S-T segment may be depressed and the T wave inverted. Right axis deviation *per se* is not diagnostic of right ventricular hypertrophy.[40] It simply reflects rotation of the QRS vector to the right of its usual position and may be seen in normals, myocardial infarction, disturbances in conduction as well as in hypertrophy of the right ventricle and even of the left ventricle The large R wave in lead V_1 has been thought to be related to rotation of the heart around its long axis so that the epicardial surface of the left ventricle faces to the right and anteriorly. In fact, it has been demonstrated that in individuals with the Tetralogy of Fallot, the right chest leads show a large R wave but direct leads from the epicardial surface of the right ventricle show a small R wave.[41] Whether or not the lie of the heart is anatomically different in those with right ventricular hypertrophy remains to be determined. It would appear from clinical and radiographic examination, that the lie of the heart is most certainly different in hypertrophy of either ventricle.

Electrocardiograms which demonstrate combined ventricular hypertrophy are seen infrequently.[42] The finding of a vertical electrical position with signs of left ventricular hypertrophy is highly suggestive but not diagnostic. The presence of large R waves in lead V_1 followed by a decreased amplitude in precordial leads to the left and then finally another rise in leads V_5 or V_6 is also suggestive, as is the presence of the P-pulmonale or P-mitrale pattern in those with left ventricular hypertrophy. However, these findings, particularly in those with non-rheumatic heart disease, do not necessarily mean combined hypertrophy. On the contrary, these changes may be present in those with unilateral ventricular hypertrophy, conduction disturbances, or myocardial disease.

Finally, in electrocardiographic parlance, the terms ventricular strain and hypertrophy are frequently employed. The diagnosis of "strain" depends upon the presence of ST-T alterations and that of "hypertrophy" upon increased amplitude of the QRS complex.[43] These terms are only descriptive and do not necessarily reflect what is present anatomically or physiologically. The terminology should be avoided for the inference is not as clear as the implication. The word "strain" when applied to individuals with cardiac hypertrophy is indefinable in the physiologic sense. Moreover, the ST-T changes can be normalized by the administration or withholding of certain electrolytes.[44]

It may be well to point out in this connection that flat or negative T deflections are noted in a number of other conditions, such as myocarditis, B-avitaminosis, hypothyroidism, alkalosis, hypokalemia, and acute or chronic cardiac compression due to pericardial disease. Extracardiac neurogenic and emotional influences play a rôle and need further study. Gallbladder disease has been held responsible. Posture occasionally plays a rôle and a flat or negative T deflection, particularly in Leads II and III, may increase in voltage or even turn positive when the tracing is taken with the patient in the recumbent instead of in the sitting position.[45]

The influence of digitalis on the ECG should be mentioned here since this drug is so commonly used in connection with cardiac enlargement. Its effect on the S-T segment consists in a depression in the limb and chest leads, usually most marked in Lead II, and in a flattening out or inversion of the T deflections. Where there is left axis deviation, however, the aforementioned segment tends to be elevated in Lead III. No very close relation exists between the degree of these changes and the amount of the drug given. *It may easily take two to three weeks, and in occasional cases up to six weeks following discontinuation of the drug for such changes to disappear completely.* If an ECG study is planned, it is important, therefore, to withhold digitalis medication, provided the condition of the patient will permit it.

Cardiac enlargement may have to be differentiated from pericarditis. In the latter condition, particularly of septic etiology, there may be an upward shift of the S-T segment in all leads.

Functional Evaluation and Prognosis: While the physiologist considers enlargement of the heart muscle as a means of adaptation, the clinician is inclined to correlate these findings with potential or actual myocardial insufficiency. Enlargement of the heart is never a complete diagnosis without determining its cause and functional status. Usually, the underlying disease can be readily ascertained by careful and thorough examination Occasionally, the cause may not be apparent. There may be an anomalous vessel or glycogenosis, amyloidosis, nutritional disturbances, muscular dystrophy, connective tissue disorders, endocardial disease, endocrinopathy, or infection. The manifestations of heart failure may be so predominant as to mask the underlying disease.

In the presence of coronary artery disease, cardiac enlargement is a much less valuable guide than in valvular disease Anginal failure is compatible with a normal heart size. Patients with coronary artery disease who develop cardiac infarction often reveal no change in heart size on follow-up studies. If this is the course of the disease, it will be found that a fairly active life is carried on much more commonly as compared with those who either had cardiac enlargement to begin with or develop cardiac enlargement subsequent to the attack.

Congestive failure rarely occurs in the presence of normal sized hearts. In this connection it should be remembered that in chronic constrictive pericardial disease the heart is sometimes prevented from increasing in size, while failure of the circulation develops sooner or later.

Patients with cardiac enlargement show, as a rule, a diminished capacity for work. The term enlargement in this connection refers mainly to the ventricular mass Considerable enlargement of the heart is likely to be followed by more or less rapid onset of failure. Auricular fibrillation sets in more frequently and the same holds true of the occurrence of thrombosis along the auricular wall or in the coronary arteries.

The general remark holds true that the larger the heart, the worse the exercise tolerance; experience with individual cases, however, shows exceptions. This holds true particularly for the younger age group who have healed rheumatic valvular lesions. It may also be stated that there is no

strict proportionality between the degree of enlargement and the signs and symptoms of heart failure. Heart size is not more than a fair prognostic criterion and the clinician never should omit obtaining a correct idea as to the general physical tolerance of a patient. Furthermore, the etiology and special anatomical features of a disease process are important items in the prognostic evaluation and should always be taken into consideration. It is known that sudden death often occurs in the presence of coronary ostium



FIGURE 7 Male, age forty-one This obese patient had developed signs and symptoms of left ventricular failure with coronary artery disease and a mild hypertension as presumable etiology A considerable degree of cardiac enlargement existed During the course of one week the patient had been given an unknown amount of digitalis The electrocardiogram (lead II) reveals sinus rhythm which is interrupted by premature ventricular beats of multifocal origin and in bigeminus
:ardia (2). These findings
and prescribing quinidine
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were not noted when all
three drugs were given together

stenosis due to syphilis, with or without associated aortic regurgitation, or in the presence of a high grade aortic stenosis and in both instances this occurs regardless of heart size. The correlation of cardiac enlargement and mortality quota seems to be closest for patients with rheumatic valvular lesions. In one such very careful study on 1164 cases, it was found that the mortality quota for all valvular lesions together for three groups of heart sizes, as determined by orthodiagraphy, was as follows: The ratio of actual to expected deaths for approximately normal-sized hearts was 420 per cent, for moderately enlarged hearts 589 per cent, and for much enlarged hearts 1092 per cent.[16]

It has been previously stated that cardiac enlargement may be stabilized over a period of years. In other instances, however, progression takes place over shorter periods of time and it is important to obtain exact information as to the rate of progression. An increase, especially if rapid, gives a poor prognostic outlook. This holds particularly true for the course of the heart in myocarditis or diphtheria.

Circulatory Failure: When cardiac enlargement is diagnosed, circulatory failure may not be present, but it will result eventually. Hence, a short discussion of this finding is justified. Those forms which are primarily of extracardiac origin will not, however, be discussed. Here belongs first the clinical picture of inflow stasis (engorgement of the systemic veins and, less common, of the pulmonary circuit) which results from inadequate work of the heart due to inadequate filling, as noted in instances of pericardial effusion, chronic constrictive pericardial disease, or with extremely high heart rate; and second, the primary peripheral failure, *i. e.*, shock.

The commonest types of cardiac insufficiency are associated with inadequate emptying of the heart. The whole heart may be affected or strain may have acted predominantly on the left or right side, resulting in syndromes which are spoken of as left- or right-sided heart failure. Before enumerating some symptoms and signs of heart failure, it must be kept in mind that one of the most important measures for a lowered circulatory efficiency is the subjective perception of the patient.

If heart failure is present, it should not be assumed a priori that the enlarged heart has reached its limit and that the prognosis is very grave. Instead, attention should be directed to uncovering some agent that may have precipitated the crisis. There may be an infection, an arrhythmia, an emotional disturbance, electrolyte or fluid imbalance, or thromboembolism. Careful examination for and proper treatment of these conditions may result in restoration of pre-existing heart size and function So-called refractory heart failure is seldom due to a diseased heart *per se*. Also, in this era of cardiac surgery, it is necessary to recognize whether the manifestations of heart failure are related predominantly to valvular, myocardial, or pericardial dysfunction.

Dyspnea: The principal factor is impairment of respiration due to engorgement of the pulmonary vessels.[47] Pulmonary congestion can be detected radiologically long before the appearance of rales The earliest clinical sign of pulmonary hypertension is an accentuation of the second pulmonic sound. Common underlying diseases affecting the left side of the heart include systemic hypertension, aortic and mitral valvular disease, and coronary artery disease. Orthopnea is present if the patient can breathe better when upright than recumbent and trepopnea if dyspnea is present in one recumbent position and less or absent in another.

Cardiac asthma or recurrent episodes of dyspnea and wheezing due to left ventricular failure is frequently associated with an antecendent history of effort intolerance. It may occur on effort or it may be precipitated by various other factors that demand a sudden increment in cardiac output Frequently, it occurs only at night after the patient has fallen asleep An antecedent nightmare may be present. The late onset in life, the absence of pre-existing allergy, the presence of cardiac enlargement, the demonstration of heart failure, either clinically or by laboratory means, and the *response to a cardiac regimen serve to differentiate it from bronchial* asthma

Cheyne-Stokes respiration is frequently seen in those with heart failure Careful observation is necessary to detect its presence. The periods of apnea may be very brief and the changes in rate and depth of respiration barely perceptible. During the periods of apnea, there may be transient unconsciousness. Prognosis should never be based upon the presence or absence of this phenomenon *per se*. Often, the discontinuance of drugs such as acetophenetidin, barbiturates or morphine will abolish this respiratory arrhythmia. Additional digitalis, restriction of salt or more frequent use of diuretics may be necessary. Treatment should be directed at both the possible underlying causes for its occurrence, and the respiratory disturbance proper (slow intravenous injection of 0 25 to 0 8 Gm. (4 to 12 grains) of theophylline-ethylenediamine).

Cardiac Pain: Pain indistinguishable from that seen in individuals with coronary artery disease may be related to heart failure.[18] After all, myocardial insufficiency may result from either impaired supply or augmented demand and the end result is the same. Nitroglycerine will offer spectacular relief if it is related to impairment of supply but will fail if there is primarily an augmented demand. In case of the latter, improvement of cardiac efficiency by digitalis or decreasing heart load by mercurials and other measures will relieve the pain. The onset of right-sided failure may be associated with a diminution or disappearance of anginal pain previously present.

Heart Sounds: A lowered intensity of the first apical sound is often and not always correctly interpreted as evidence for heart muscle dysfunction. Leaving aside the possible influence of obesity or emphysema, it must be remembered that a relatively longer, though still normal atrioventricular conduction time (for instance, 0.20 sec.) tends to be associated with a first sound of lesser intensity. A similar and more marked effect is caused by mitral insufficiency, and also by aortic stenosis on the second aortic sound. Besides mitral disease, an accentuation of the second pulmonic sound is noted with left-sided failure, whatever the etiology may be.

Gallop rhythm, a form of triple rhythm, is characterized by the appearance of a third heart sound, diastolic in time and usually dull in character.[19] It is best perceived by auscultation, but can be seen and felt as well. Gallop rhythm is likely to disappear with a slowing of the heart rate, and is not heard with auricular fibrillation although graphic registration seems to indicate it may exist with the latter condition. Mitral lesions tend to obscure it Gallop rhythm indicates, as a rule, failure of the left ventricle only, unless it accompanies acute myocarditis or pulmonary embolism. The presence of gallop rhythm entails, as a rule, a bad prognosis but this does not necessarily hold true if it is observed in the presence of acute myocarditis where it indicates a toxic damage of the heart muscle which may be reversible. It is to be emphasized that a diagnosis of heart failure should not be based upon the presence of gallop rhythm alone.

Blood Pressure: The effects of heart failure have a variable influence. Cardiac infarction is commonly followed by a fall, while a rise, sometimes to a very marked degree, may be noted during an attack of angina pectoris or pulmonary edema. A moderate rise with each bout of failure is noted in occasional patients. It should be noted parenthetically that high blood pressure does not contraindicate the use of digitalis.

During the measurement of the blood pressure, alternation may be observed as a succession of strong and weak beats. The loud sounds come through corresponding to only half the heart beats. This finding should not be confused with an extrasystolic bigeminus. An alternating pulse is not uncommonly encountered in patients with arterial hypertension. Its presence, particularly when continuous in nature, signifies heart failure.

Cyanosis: It is closely correlated with an increase in the amount of reduced hemoglobin; anemia, therefore, tends to counteract the appearance of cyanosis. It may be present in certain congenital cardiovascular malformations without indicating failure. In acquired lesions, cyanosis will be

noted particularly in the presence of mitral stenosis, tricuspid stenosis, and with right-sided failure in general. It is very marked if due to extensive obliterative vascular disease in the lesser circulation. Cyanosis may occur, of course, without any cardiac disease; pulmonary hypo-ventilation serves as an example. An appearance clinically indistinguishable from that produced by reduced hemoglobin is that observed in the presence of methemoglobinemia or sulfhemoglobinemia. One sees patients with hypertensive cardiovascular disease who are markedly cyanotic following the prolonged ingestion of proprietary preparations containing acetanilide for the relief of headache. Marked cyanosis in the absence of dyspnea should incite suspicion of chemical poisoning.

Pulmonary Engorgement: Left-sided failure or obstruction leads to engorgement of the venous half of the pulmonary circuit, and later this is followed by overfilling of the entire lung field. Examples are hypertension and organic defects of the left-sided valve orifices. The output of the left and right heart are equal for some time and circulation takes place at a higher pressure level. The outstanding symptom is dyspnea, both of the exertional and paroxysmal variety. Cyanosis, cough, hemoptysis, and fine basal rales may or may not be present. Signs for pulmonary engorgement are: First, the roentgenogram reveals the transparencies of the lung fields diminished, with occasional cloudy opacities; all vascular shadows are increased in density and width, but relatively hazily outlined. This holds particularly true for the hilus structures. Second, an accentuation of a previously normal second pulmonic sound. Third, a decrease in the velocity of blood flow through the pulmonary circuit; this can be determined by measuring the arm-to-tongue and arm-to-lung circulation time

Venous Engorgement: Right sided failure or obstruction leads to engorgement of the systemic veins. An increase of the venous pressure to over fifteen cm of water indicates, then, advanced insufficiency of the right side of the heart, provided that pericardial and mediastinal pathology have been excluded. Such insufficiency of the right heart may be primary in nature, such as observed with emphysema, pneumonoconiosis, obliterative disease of the pulmonary arteries, pulmonary embolism, and organic defects of the right-sided valve orifices Much more commonly, however, it follows failure or valvular lesions of the left side Signs for venous engorgement are cyanosis, engorgement of superficial veins and increase in venous pressure, swelling of the liver, subcutaneous edema and ascites.

The normal venous pulse, both of liver and neck veins, is a volume pulse and indicates dynamic events in the right atrium. As one observes the movements along the neck veins in a healthy person in the recumbent position, one easily notices a collapse which is ventricularsystolic in time. This collapse is due to the rapid inflow of blood into the previously emptied right atrium. The caudad movement of the atrioventricular septum and the sudden drop of the intrathoracic pressure due to outflow of blood from the chest cavity favor this collapse. The veins then fill gradually. This ascent is broken by another collapse, which occurs during the early part of ventricular diastole This collapse is due to the emptying of blood from the right atrium through the opened tricuspid valves, and, while always

registered on the graph, it may not be noticeable on gross inspection. The progressive distention of the vein is then suddenly increased. This indicates atrial systole, which has interrupted the inflow of venous blood into the right atrial cavity. The normal venous pulse in the neck, therefore, is characterized by a systolic emptying and diastolic filling. Proper timing should be carried out by palpating the carotid or the radial pulse while inspecting these pulsations.

With cardiac failure and mild congestion the veins reveal an increase in both fulness and pulsations. Occasionally, in those with heart failure, the cervical veins may not be distended and the venous pressure may be normal. In such individuals, increased abdominal pressure, usually exerted in the region of the right upper quadrant, will result in distention of the cervical veins and a rise in the venous pressure. Of course, it is necessary to be certain that the patient has not held his breath during this maneuver, for similar changes may occur with a Valsalva experiment. As congestion increases, the normally visible pulsations in the lower part of the neck disappear, while they become noticeable in its upper part; and pressure against the abdomen causes the level of pulsations to climb craniad. With maximal stasis, no movement may be noted in the very full veins, and pulsations may be only brought out as the patient gradually sits up or during deep inspiration. A closer observation of these pulsations reveals that the normally observed systolic collapse is lacking completely. That means that the ascent of the venous pulse, starting in early diastole, lasts throughout the systole. Hence, one speaks of the systolic or ventricular form of the venous pulse. Obviously, the enhancing effect of ventricular contraction on the venous blood flow is diminished; and the overdistended and often fibrillating right atrium is emptied inadequately. A collapse from the high plateau occurs at the time of the opening of the tricuspid valves, which is during the early part of ventricular diastole. Hence, this pulse is characterized by a diastolic emptying. In the presence of tricuspid regurgitation there is likewise noted a diastolic collapse and a systolic elevation. But the latter is more impressive, abrupt, and, in contrast to the congestion pulse, well palpable

A congested and large liver is likely to reveal pulsations of the ventricular type, particularly so in the presence of auricular fibrillation. The ascent of the pulse wave is not so distinctly felt, but rather the subsequent diminution in volume, *i. e.*, the diastolic emptying of the liver. This is also, and quite markedly, noted in the presence of adhesive pericardial disease. This is of diagnostic significance, because the condition, which is most likely to imitate adhesive pericardial disease, is tricuspid regurgitation. Here a liver pulse of the ventricular type is likewise found, but the outstanding feature is a sudden and forceful systolic thrust; while with ordinary congestion and adhesive pericardial disease the systolic filling of the liver takes place gradually. In the presence of sinus rhythm, and providing the right atrium is still capable of contracting forcefully, with the right heart overfilled or because of an associated tricuspid stenosis, an obstacle is offered to right atrial emptying. The blood is then backed up into the venae cavae during the presystolic period and a presystolic re-

gurgitation wave results. This is called the presystolic auricular liver pulse, *i. e.*, it is diastolic in time and its elevation distinctly follows the elevation palpated at the radial artery. In the presence of mitral stenosis such a presystolic liver pulse is highly suggestive of an associated tricuspid stenosis, though it may well occur in the presence of marked congestion with sinus rhythm preserved. Often the liver pulse reveals in addition to the presystolic regurgitation wave a systolic elevation. An associated tricuspid insufficiency or marked overfilling of the right atrium, such as noted in tricuspid stenosis or with the interatrial septal defect, may be responsible for it.

Treatment. Reversibility of Cardiac Enlargement: Cardiac enlargement, as previously stated, signifies potential or actual insufficiency of the myocardium and patients with a considerable degree of enlargement rarely ever possess good exercise tolerance. It is the duty of the physician, therefore, to *regulate the life of the patient* so that he will remain within the limits of his reserve, in order to avoid heart failure as long as possible Such a limitation of activity may range from complete *bed rest*, as in the case of acute myocarditis, glomerulonephritis, or congestive failure, to a program of nearly normal activity, avoiding athletic and competitive activity and excessively long working hours, as in the case of a fully compensated rheumatic valvular lesion or benign essential hypertension. *Overweight* should be corrected. *Digitalis* is first indicated when the limitation of reserve becomes evident, together with simultaneous *curtailment of physical activity*, and second, when auricular fibrillation supervenes, particularly in the rheumatic and sclerotic group.

In the great majority of instances enlargement of the heart is a chronic incurable condition, particularly in reference to the large group of hypertensive, valvular, sclerotic, or syphilitic etiology

In a relatively few instances it is possible to remove the cause of cardiac enlargement so that regression of heart size will occur, provided that not too long a period of time has elapsed and that no other complicating factors interfere As examples may be cited. (*a*) Prolonged attack of paroxysmal auricular tachycardia (unilateral carotid sinus and bilateral bulbous pressure; induced gagging and vomiting; *magnesium sulfate*, 15 cc. of a twenty per cent solution, intravenously; *quinidine sulfate*, 0.4 to 0 6 Gm. (6 to 9 grains) orally, or *quinidine hydrochloride* with *urea* and *antipyrine*, 0.6 Gm. (9 grains) intramuscularly, every four hours; *mecholyl*, 20 to 30 mg. (⅓ to ½ grain) subcutaneously (atropine sulfate is the antidote); *digitalis*—in the form, for example, of digitoxin, 0.4 mg. ((1/150 grain) to be repeated within a few hours); paroxysmal ventricular tachycardia (*magnesium sulfate, quinidine sulfate*, as above; pronestyl; 100 mg. per minute IV); (*b*) thyrotoxicosis (*subtotal removal of the gland or radioactive iodine*); (*c*) B-avitaminosis (purified B_1-*vitamin* intravenously and orally and proper *diet*), (*d*) anemia of the pernicious or intestinal-parasitic type (*liver*, or B_{12} intra-muscularly); (*e*) arteriovenous fistula (*operative closure*).

In other instances, a considerable diminution in the heart size will be noticed, provided the natural course of the disease is favorable, though

treatment may occasionally be helpful. To cite: (*a*) acute glomerulonephritis with hypertension (here resorption of pericardial fluid may be a contributing element in the regression of "heart" size); (*b*) myocarditis of rheumatic fever, diphtheria, grippe, typhoid fever; (*c*) replacement of a previously slow heart rate (nodal rhythm, complete heartblock) by a faster, normal heart rate; (*d*) pulmonary embolism (said to affect the right heart only).

In the hypertensive patient with evidence of left ventricular failure, one occasionally observes regression of heart size, under the effect of rest, low sodium diet, and digitalis. Somewhat more often a reduction in heart size is noted when the blood pressure has been permanently lowered secondary to a dorsolumbar sympathectomy regardless of whether or not left ventricular failure was present to begin with. In the absence of heart failure, regression of cardiac enlargement in those with hypertension may occur with many and varied regimens including rest, salt restriction, salt diuresis, hypotensive agents and surgery.

It may be noted that in healthy athletes a moderate increase of the heart size may be observed during the period of severe training. This takes about four to six weeks and recedes at about the same rate following cessation of training. Whether the process underlying the increase in heart size is only due to a stretching of the muscle fibers, or whether there is also a thickening, is not known.

Finally, it may be asked how often and how much the heart recedes in size with recovery from congestive failure. The change in the height of the diaphragm resulting from a diminution in the total bulk of the abdominal contents causes a change in the shape and position of the heart, and this is a real obstacle in an evaluation on decrease in size, both from an x-ray and clinical point of view. In addition, resorption of pericardial fluid may introduce an element of error.

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MORRIS W. STROUD, 3RD, M.D.

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Congestive Heart Failure

Introduction: The purpose of this chapter is to describe briefly and concisely a very common clinical condition—congestive heart failure. To do this various aspects must be discussed which include the mechanism, complicating factors, signs and symptoms, differential diagnosis, prevention, and therapy. A tremendous amount of clinical and basic work has been done over the years without eliciting the exact mechanisms that bring about congestive heart failure, nor a complete and concise understanding of exactly how the many therapeutic agents employed in this condition perform their functions. However, it is worthwhile to review the more generally accepted present day concepts bearing on this subject.

The Mechanism of Congestive Heart Failure: As pointed out in many recent articles and textbooks, two diametrically opposed schools of thought concerning the mechanism of heart failure have existed for generations. These two factions have been called the schools of forward failure and of backward failure. Those who believe in forward failure argue that the main cause for congestive heart failure is insufficient output of the heart to the tissues. The other school believes it is due to congestion of parts of the body, or backward pressure from the failing ventricle(s) Extensive recent studies in many laboratories favor the forward failure school of thought in the vast majority of cases of slowly progressing congestive heart failure.

Occasionally, the classic picture of sudden backward failure is observed. A typical example would be the sudden appearance of pulmonary edema following a massive myocardial infarct in a patient with no previous history of dyspnea. In such a patient edema of the lungs develops suddenly without a change in body weight. The fluid collected in the lungs comes from fluid originally present in the blood stream and from fluid pulled into the blood stream from the tissues This represents an abnormal redistribution of the fluid normally present in the body. It is not due to salt retention and increased body fluids.

There are several important findings present in patients with congestive heart failure who gain weight from the accumulation of body fluids, as recently reviewed by Stead.[1] (1) A marked reduction of the renal excretion of sodium chloride, (2) a higher urinary output during the night than during the day, (3) an unimpaired ability to excrete water without difficulty at a maximal rate and an ability in moderate congestive failure, if salt is withheld, to excrete water sufficiently well to tolerate a daily fluid intake of several liters, (4) a frequent and moderate lowering of the con-

centration of sodium and chloride in the blood, (5) an increase in the plasma and blood volume, and (6) an elevated venous pressure.

Sodium chloride retention is a characteristic finding in chronic congestive heart failure. This inability to excrete salt is relative rather than absolute, and the patient with heart failure varies his sodium chloride excretion as does a normal subject. The only peculiarity shown by a patient with heart failure is that he excretes more salt at night than in the daytime. Presumably the daytime activities divert some blood flow from the kidneys as occurs during exercise in normal people. The decreased renal blood flow that is uniformly found in subjects who form edema at rest on an unrestricted diet is the most likely cause for the edema and salt retention. With the reduced renal blood flow, total glomerular filtration is decreased, although the amount of filtrate obtained from each unit of plasma flowing through the glomeruli is greatly increased. The lowered filtration rate decreases the amount of sodium chloride presented to the tubules over a given period of time. The tubule reabsorbs nearly all of the filtered sodium chloride. However the absolute amount of sodium chloride filtered is so small that the total amount of sodium chloride reabsorbed is much less than in normal persons. Thus, in chronic congestive heart failure the renal blood flow and filtration rate is decreased; the per cent of sodium chloride reabsorption by the tubules is increased; and the urinary excretion of sodium chloride is reduced. It should be emphasized that the disturbed renal hemodynamics of chronic failure are not correlated with changes in various pressure, but do correlate with the reduction of cardiac output.

Many objections have been raised to the glomerular-tubular imbalance concept of sodium retention. For instance, many investigators believe that the damming up of blood behind the failing ventricles forces water into the tissues by increasing venous and capillary pressure. Thus, ingested salt and water pass through the blood stream to the tissues and are not excreted by the kidneys because of prerenal deviation. Some arguments against this theory are that it fails to account for the similar retention of salt which occurs after hemorrhage or trauma; that plasma and blood volume in chronic congestive failure is increased rather than decreased; and that the quantitative difficulties in handling sodium chloride persist after the venous pressure has been returned to normal by salt restriction and diuretics.

Other investigators have felt that the impairment of sodium chloride excretion results from high venous pressure in the kidneys produced by backward failure. This has been shown to be true in animal experiments where there is a decrease in sodium chloride output from a rise in venous pressure, without perceptible change in renal blood flow or filtration rate. This does not explain the abnormal sodium chloride retention in man that persists after the return to normal central venous pressure, nor does it explain similar retention of sodium chloride after hemorrhage.

Another objection to the glomerular-tubular imbalance concept is the fact that some other diseases such as chronic glomerulo-nephritis and marked nephrosclerosis do not cause the same tendency to edema so char-

acteristic of congestive heart failure. Stead[1] points out that this observation actually supports the concept as there is usually a decrease in tubular as well as glomerular function in these renal diseases. On the other hand, the tubular function remains surprisingly good in congestive heart failure.

In other words, the argument is that a fairly even and equal decrease in glomerular filtration and in tubular function because of disease will decrease the tendency for edema formation.

With the tremendous interest in the salt retention brought about by ACTH, cortisone, testosterone and other corticosteroids, some investigators wonder whether a major cause for salt retention in congestive heart failure might not be hormonal influence upon the renal tubules produced by decreased circulation in the pituitary and adrenal glands. There is some indication that there is increased urinary excretion of corticoids. Studies of sweat secretion are compatible with this thesis. Undoubtedly the decreased cardiac output does stimulate the pituitary-adrenal axis, but it is highly doubtful that such stimulation plays much of a part in congestive heart failure. It remains to be shown that the body produces sufficient salt-retaining hormones such as aldosterone to cause the massive edema of chronic heart failure.

In summary, the basic mechanism of congestive heart failure is the decreased cardiac output produced by organic heart disease. The decreased cardiac output in turn produces a decrease in renal blood flow and renal glomerular filtration rate. In the face of normal tubular reabsorption there is a quantitative decrease in sodium chloride excretion With unrestricted fluid and electrolyte intake sodium chloride retention occurs and the extracellular space expands producing increased fluid retention and the eventual production of clinical edema. It remains to be shown whether the stress of congestive failure produces unusually large amounts of salt-retaining hormones. In acute congestive heart failure brought about by myocardial infarction and similar conditions, pulmonary edema develops suddenly without a change in body weight due to an abnormal redistribution of the fluid normally present in the body.

Signs and Symptoms: The cardinal symptom of myocardial insufficiency is dyspnea on exertion or at rest. Various tasks that formerly caused no symptoms now produce shortness of breath. If the individual has led a very sedentary life, or if his activities have been severely restricted because of disabilities, the first symptom may be dyspnea that comes suddenly at rest, particularly at night As the degree of myocardial insufficiency increases, dyspnea occurs with less physical effort until finally it is present even at rest. Dyspnea of such severity as to render lying flat in bed difficult or impossible is called orthopnea. At this point Cheyne-Stokes breathing is usually present. As the condition progresses moist rales appear first at the lung bases and later throughout the lungs There may be attacks of paroxysmal cardiac dyspnea attended by asthmatic breathing (cardiac asthma) or by acute pulmonary edema with copious frothy and frequently blood stained expectoration. All these signs and symptoms are due to congestion in the pulmonary circulation.

In the earliest phases of left ventricular failure described in the preceding paragraph, there may be no overt signs or symptoms. However, the vital capacity of the lungs is already diminished; circulation time from arm to tongue may be slightly prolonged; and there are almost invariably signs of heart disease as manifested by cardiac enlargement and significant heart murmurs. At this point X-ray studies of the chest will not reveal pulmonary congestion as commonly believed. The butterfly distribution of pulmonary congestion and signs of fluid in the chest usually occur only with frankly overt physical signs and symptoms. Other findings that usually occur late in the disease are a diastolic gallop rhythm and pulsus alternans.

The early evidence of congestion of the greater circulation is increased venous distention and/or dependent edema. In the earlier stages of failure, venous pressure may be within normal limits during rest and only become elevated during exertion. Therefore a normal resting venous pressure does not necessarily indicate cardiac competence or an ability to do work under stress. On the other hand increased venous pressure at rest implies a moderate degree of fluid retention in the extracellular space. The appearance of edema in the ambulatory person occurs in the morning and increases during the day only to disappear at night.* In the bedridden patient the first appearance of clinical edema may be over the sacrum, the most dependent portion of the body. Unfortunately, the first appearance of edema that pits on pressure does indicate that excessive fluid has already accumulated. It has been demonstrated in actual practice that the patient goes from his basal weight level to the clinical appearance of edema through a stage in which fluid is insensibly collected and only manifested by an increase in body weight. It has been stated that there must be a ten per cent increase in body weight before clinical edema appears. Therefore, in a patient in whom congestive heart failure is suspected or in whom it has occurred before, a definite weight gain from five to ten pounds within a short period of time indicates increasing congestive heart failure. As a part of the congestion in the greater circulation, venous pressure increases, the jugular veins distend, and the liver enlarges. Associated with this congestion in the splanchnic area are symptoms of epigastric distress, nausea, food intolerance, and other gastrointestinal symptoms. Palpation of the liver will reveal an enlargement below the xyphoid and/or the costal margin often accompanied by pain on pressure.

There are other symptoms which generally accompany heart failure. They are less distinctive and are commonly found in other conditions unassociated with heart failure. These symptoms include weakness, easy fatigability, irritability, indigestion, insomnia, and dull aching precordial pain. Alone such symptoms are of little value in establishing the diagnosis of congestive heart failure.

Although congestion in the lesser and greater circulations can occur separately, they are much more commonly found together. As a result, all

* As fluid retention increases, edema will not disappear. Stasis, infections and increasing fibrosis of the subcutaneous tissues are normal sequelae

combinations of the above symptoms and signs may be elicited. Thus, the usual picture of early combined failure consists of dyspnea, orthopnea, a few moist rales at the lung bases more particularly on the right, distention of the neck veins, slightly enlarged liver, and from one to two plus pitting edema of the ankles and feet more noticable in the afternoon. Although rales usually are heard first at the right lung base and later at the left base, the reverse can occur. Pleural effusions do not appear if the visceral and parietal pleural membranes are fused by antecedent disease. The full blown picture of combined failure is as follows: The patient is orthopneic and the neck veins are obviously distended above the heart level Respiration is markedly increased and often of the Cheyne-Stokes type. Moist rales are heard in the chest extending from the bases to the fourth or fifth interspace. Other findings are dulness to percussion and evidence of fluid at both bases; *gallop rhythm;* cardiac enlargement on inspection and by percussion; the liver edge three to four fingerbreadths below the xyphoid and/or the right costal margin; more or less fluid in the abdomen as manifested by shifting dulness; four plus pitting edema of the legs, lower abdomen, and scrotum; and visible cyanosis of the face and extremities but particularly the nail beds and tongue. Blood pressure is usually normal but may be somewhat elevated. Pulsus alternans may be revealed by palpation of the radial pulses or with the sphygmomonometer. Finally there may be a slight icteric tint to the sclerae and skin due to impaired liver function.

Differential Diagnosis: One of the most important features in the treatment of congestive heart failure is the recognition of conditions that may simulate it. Too, some disorders may produce congestive heart failure as a secondary manifestation. In the latter type of dysfunction the treatment of the primary disease is much more important than the treatment of the manifestation. All too frequently digitalis and diuretics are unnecessarily administered to patients who are thought to have congestive heart failure. Hypotension, tachycardia, dyspnea, rales in the chest, and edema often are due to causes other than congestive heart failure.

These conditions can be roughly divided into two groups. The first group consists of the diseases and manipulations that cause peripheral circulatory failure or shock. Such conditions include infectious diseases, severe hemorrhage, severe trauma, diabetic acidosis, cerebral hemorrhage, surgical operations (particularly with prolonged anesthesia), conditions producing pulmonary emboli, and conditions which cause severe respiratory embarrassment such as emphysema, asthma, and other pulmonary disorders. Unless there is an element of congestive heart failure in association with these diseases, the usual therapeutic measures for congestive heart failure are of no avail.

The second group consists of conditions associated with "high output failure." In these the manifestations of congestive heart failure often coexist with the primary disease Among this group can be included severe anemias, nutritional deficiencies, hyperthyroidism, and arteriovenous fistulas. Other miscellaneous conditions consist of myxedema, renal disease,

lymphangitis, thrombophlebitis of the lower extremities, marked obesity, and supramediastinal obstructions. These conditions may also serve as complications of primary congestive heart failure.

The diagnosis of congestive heart failure should not be made unless definite signs and symptoms are present. In doubtful cases a therapeutic trial of digitalis is worthwhile. Differential diagnosis is aided by measuring vital capacity, body weight, circulation time, and venous pressure before and during digitalization.

Diagnosis of Some Surgically-Remediable Conditions: Although the diagnosis of these conditions are presented more fully in other chapters, it is worthwhile to present a few of the characteristic features of some of the congenital and acquired cardiovascular lesions that may produce congestive failure and which may be improved or corrected surgically.

Pure Pulmonary Stenosis: Usually the child afflicted with this congenital lesion lives only six to eight months. In the milder forms the clinical features are dyspnea, marked limitation of activity, progressive right ventricular enlargement, and fulness of the pulmonary conus of the right ventricle. Cyanosis varies with the patency of the foramen ovale. A systolic murmur and thrill over the pulmonary area occurs almost invariably. The electrocardiogram shows marked right axis deviation. An abnormally short circulation time occurs only with a patent foramen ovale.

Lutembacher Syndrome: This congenital disorder is an atrial septal defect combined with mitral stenosis and enormous dilatation of the pulmonary artery. It occurs twice as often in women as in men. Life expectancy is about forty years. Suspicion should be aroused upon seeing an asthenic person of poor physical development with conspicuous left-sided chest deformity, but without cyanosis or clubbing. The important physical findings are a basal systolic murmur, intermittent paroxysmal auricular tachycardia, and signs of mitral valvular disease. The distinctive x-ray features are increased hilar shadows, great right atrial and right ventricular enlargement, a small aortic knob, and a prominent pulmonary conus Tall P waves, a prolonged P-R interval, right axis deviation, and QRS changes are the usual ECG findings.

The Maladie de Roger: Roger was the first to describe the simple perforation in the ventricular wall. Roger's disease differs from a high ventricular septal defect which is caused by a failure of the aortic septum to meet the ventricular septum. The latter may occur alone or when the aorta over-rides the ventricular septum. The maladie de Roger is usually asymptomatic and is discovered upon routine physical examination. A harsh systolic murmur and thrill are found in the third and fourth left interspaces close to the sternum. Surgery is rarely required.

Patent Ductus Arteriosus: This congenital lesion is usually easy to diagnose clinically. Very infrequently, it may need to be distinguished from the murmurs of severe anemia and a venous hum often heard in childhood. Almost invariably a continuous or so called "machinery" murmur is found over the pulmonic area (second left interspace) with a systolic accentuation and widened pulse pressure. When a systolic murmur without any diastolic component is found in this area, it can be rarely diagnosed as

patent ductus arteriosus. Not all individuals with this lesion need surgery. The patient should be checked periodically for signs of progressive cardiac failure associated with symmetrical ventricular enlargement.

Coarctation of the Aorta: There are two distinct types, infantile and adult. In the former, the patent ductus arteriosus remains patent. The *adult type* occurs much more frequently in males and the constriction is found usually just proximal to the ductus arteriosus. The clinical findings in the strikingly well-developed male are the difference in strength of the pulse and blood pressure between the upper and lower extremities. The *right radial pulse is often greater than the left because of constriction of* the left subclavian artery. Blood pressure and arterial pulsations in the lower extremities are greatly diminished. The extensive collateral circulation produces murmurs and pulsations not found in the normal person. The most common places where these findings occur are the intrascapular area and over the internal mammary arteries. The X-ray often reveals notching of the ribs due to the enlargement of the internal mammary arteries. This finding is rarely seen before twelve years of age. X-rays often reveal a dilated aortic knob. Finally, poor and delayed healing of leg wounds in normal appearing tissue should arouse suspicion

The *infantile type* is usually incompatible with life beyond early infancy and is difficult to diagnose.

Arteriovenous Fistulas: The congenital form usually occurs in the extremities and rarely causes cardiac failure. Large fistulas in the lungs may cause cardiac embarrassment. They are diagnosed by the presence of X-ray shadows and a murmur heard locally, if the site of the fistula is near the chest wall.

The acquired type of arteriovenous fistula, if large, may cause marked cardiac embarrassment and congestive failure. The diagnosis is usually simple. It depends upon the following findings: the presence of unexplained unilateral varicosities; one limb longer or warmer than the other; increased oxygen saturation of the venous blood from the site of the lesion; evidence of venous insufficiency after an injury, the patient's awareness of a murmur in the region of a penetrating wound; the finding of a continuous machinery-like thrill and bruit (increased in intensity during systole); and the sharp decrease in pulse rate when the fistula is closed by digital pressure (Branham's sign).

Acquired Cardiac Valvular Defects: The most important lesions are mitral and aortic stenosis. Surgical intervention, as discussed elsewhere in this book, can produce dramatic results The signs and symptoms of these valvular lesions are described in Chapter 17.

Therapy of Congestive Heart Failure: The important therapeutic measures in the treatment of congestive heart failure are rest, relief from pain or discomfort, digitalization, restriction of sodium ingestion, and diuretics. The prevention and treatment of complications that aggravate congestive heart failure are discussed in succeeding sections

Restriction of Activities: One of the most important measures in the treatment of patients with congestive heart failure is the restriction of activities by confinement to bed and chair. The effectiveness of such a re-

gime is well illustrated during the clinical evaluation of one of the digitalis preparations when no other therapeutic measures are used. If a patient's activities are markedly restricted, it may take ten to fourteen days to reach a state of equilibrium. In the patient in congestive heart failure with auricular fibrillation the ventricular rate will slow and there may be a spontaneous diuresis of ten, to thirty pounds of fluid with a concomitant weight loss. Under the "hurry up" modern methods of treatment for congestive heart failure in which bedrest, digitalization, low salt diet, and diuretics are employed simultaneously, this factor is often overlooked. The restriction of activities will increase renal blood flow, glomerular filtration rate, and thereby the urinary output of sodium.

The social and economic aspects of the individual patient must be taken into consideration in this respect. In very mild congestive failure with minimal edema and weight gain, a few days' restriction to the bedroom with bathroom privileges may be employed rather than continuous bedrest. With evidence of moderate congestive failure, bedrest will hasten the rehabilitation of the patient. As in myocardial infarction, bedrest should not imply absolute immobility. The patient should be encouraged to move around and flex the muscles to prevent peripheral stasis and thromboembolism. Self-feeding, shaving, and frequent turning should be encouraged. If a comfortable chair can be provided, there is no reason why the patient should not spend most of the waking hours in it. Some find it more comfortable to even sleep in the chair. The use of a bedside commode rather than a bedpan is to be encouraged. Normal evacuation is much more likely and oxygen consumption is significantly reduced with the use of a bedside commode as compared to a bedpan. In the presence of peripheral venous thrombosis the straining on a bedpan may easily induce pulmonary embolism.

Patients with congestive heart failure in general fare better in the upright position. This is particularly important as the horizontal position favors the accumulation of fluid due to the reabsorption of edema from the legs. As the lungs instead of the legs become the most dependent portion of the body, pulmonary edema and stasis pneumonitis may result. The upright position enhances drainage of the urinary tract and the ability to void. The likelihood of urinary infection and calculi are decreased. A simple measure to prevent paroxysmal nocturnal dyspnea is the placement of blocks eight to nine inches high under the head posts of the bed.

Under restriction of activities may be included a low caloric diet in the overweight patient. Semistarvation produces a fall in blood pressure, pulse rate, and basal metabolic rate. These changes will diminish the work of the heart and thereby improve the circulation. With moderately severe congestive heart failure the simple Karell diet consisting only of 200 cc. of milk four times daily, but allowing additional water up to two or three liters daily, may be employed for two or three days. Afterwards a more general diet containing the proper amount of vitamins is gradually allowed. A diet allowing 1 Gm. of protein per kg. body weight per day is permissible unless there is real evidence of severe nephritis or cirrhosis.

Under the restriction of activities, sedation should be included. The

orthopnea, dyspnea, and general discomfort of patients with moderate congestive failure may be combated by continuous sedation. It may be advisable to give 10 to 15 mg. (1/6 to ¼ grain) of morphine sulfate subcutaneously for the first few nights. This dose should be gradually diminished and in four or five days phenobarbital 60 to 90 mg. (1 to 1½ grains), pentobarbital in the same dosage, or chloral hydrate 1.0 Gm. (16 grains) may be given to induce sleep. Daytime sedation such as phenobarbital 15 to 30 mg. (¼ to ½ grain) may be used three times daily.

Excessive use of barbiturates and analgesics may be dangerous in cor pulmonale or in serious liver disease. In cor pulmonale there is an elevation of the carbon dioxide tension (pCO_2) which is aggravated by medication that depresses the respiratory center. Confusion, diminished ventilation, and even death may occur. Severe liver disease prolongs the action of these drugs.

Other measures to induce rest consist of mild cathartics or enemas if constipation is present after two to three days. In the presence of pychoses which are often associated with severe heart failure, all sedatives should be withheld. During the early period of recovery visitors should be restricted, although diversions such as reading, listening to the radio, watching TV, and writing letters help relieve the boredom induced by the physical restriction.

Digitalis: The mode of action and therapeutic uses of digitalis whole leaf, the glycosides derived from the digitalis plants, and other cardiac glycosides are described in greater detail in Chapter 17. Briefly, digitalis is the only drug in present use which has a specific action upon congestive heart failure. In congestive heart failure the myocardium is dilated both in systole and diastole. Digitalis is the only known drug that can shrink the heart size to within normal limits. If medication is carried to excess in diseased hearts, the systolic and diastolic sizes are further reduced. Efficiency is lost and congestive phenomena may reappear. Digitalis administration reduces the reserve of normal hearts. In patients suffering from auricular fibrillation, digitalis delays conduction through the AV node and slows the ventricular rate. It is the drug of choice for congestive heart failure. It increases tonicity and contractility of the damaged myocardium.

The milder forms of congestive failure can be handled by digitalis administration alone It is only in the more severe forms that salt restriction, mercurials, or other forms of therapy need be employed In recent years there has been an increased incidence of digitalis toxicity, iatrogenic in origin. In actual practice digitalis is a relatively safe drug as its therapeutic range is about two-thirds of the dose required to produce toxic symptoms. The most important point about digitalis therapy is the avoidance of toxicity. It is the RARE patient that needs rapid digitalization. The overwhelming majority of patients can be digitalized over a period of days if the general principles of restricted activities and the judicious use of mercurials or a sodium restricted diet are followed The patient with mild congestive failure can be given .1 Gm. of the whole leaf (1½ grains) or digitoxin 0.1 mg. three times a day for five days, and then re-evaluated clinically. In the few instances where moderate haste is necessary, the pa-

tient may be digitalized in two or three days if kept under constant observation. The whole leaf 0.3 Gm. (4½ grains) or digitoxin, 0 3 mg. may be given every six hours. The patient should be evaluated before each new dose.

The most common toxic signs are the appearance of frequent premature ventricular beats and coupling. The most common symptoms are gastrointestinal. Nausea, vomiting, and diarrhea occur as the toxic dose is approached. The signs and symptoms of improvement are weight loss, and the disappearance of dyspnea, orthopnea, peripheral edema, engorgement of the liver, abdominal fluid, rales, and pleural effusion. In congestive failure associated with auricular fibrillation, the slowing of the ventricular rate from around 140 to 170 to a rate between 60 to 80 is a very helpful guide to therapy. The premature ventricular beats associated with uncontrolled auricular fibrillation disappear as the ventricular rate is controlled. During the early stages of digitalization the ventricular slowing is due to the vagal effect, and later to the direct effect upon the conduction tissue of the heart itself.

In the rare patient critically ill with acute congestive failure, intravenous digitalization may be employed *cautiously.* In such cases no more than one half of the digitalizing dose of the drug should be given. Toxic effects from unsuspected previous digitalization, electrolyte imbalance, and unusual sensitivity may thus be avoided. The intravenous preparation of the whole leaf, digalen, may be given in a dosage equivalent to 0.8 Gm. (12 grains) of the whole leaf. Similarly 0.8 mg. of digitoxin may be employed. Ouabain or strophanthin, which are the fastest acting glycosides, may be given in doses of 0.3 to 0.5 mg. and 0.5 to 0.75 mg. respectively. It is safer to wait at least four to six hours before giving any further digitalis regardless of the preparation. Although complete digitalization will not be accomplished by this method, the patient's life will not be jeopardized. Concomitant measures such as oxygen, morphine, and immobilization will help in producing the rapid abatement of the symptoms and signs.

Unless it is certain that digitalis has not been given previously, discretion is the better part of valor and one should proceed to digitalize cautiously. It should be pointed out that *myocardial infarction is not a contraindication to the use of digitalis in the presence of congestive heart failure.*

Digitalis dosage must be tailored to the individual. Therefore no rule of thumb will suffice for either the amount of drug needed for digitalization or for daily maintenance. In about fifty to seventy-five per cent of patients 1.5 Gm. (22½ grains) of digitalis and 1.5 mg. of digitoxin will fully digitalize. In a similar percentage of patients the average maintenance dose for each drug is approximately one-tenth of the digitalizing dose, digitalis 0.15 Gm. (2 grains) and digitoxin 0.15 mg. It is the author's opinion that in most instances the whole leaf preparation should be tried first. Only after an unsuccessful therapeutic trial of the whole leaf should one of the purified glycosides such as digitoxin, digoxin or gitalin be employed. Every three to six months it may be necessary to reevaluate a patient on a maintenance dose in order to avoid toxicity or underdigitalization. For-

tunately, once a maintenance dose is established it usually can be maintained for years without need for adjustment. Some patients seem to do better on certain preparations than others as far as gastrointestinal tolerance is concerned. In the vast majority of patients this is purely emotional. Another very important point is that patients do not develop tolerance to digitalis. Rather, if the congestive failure increases, it is due to dedigitalization or to progression of the disease. Finally, sensitization to digitalis preparations occurs rarely, if ever.

Diuretics: In many instances of congestive heart failure digitalis combined with restricted activities causes sufficient diuresis to produce an edema free state. As the disease progresses in severity these measures are not sufficient to prevent accumulation of body fluid and visible edema. In acute severe congestive heart failure precipitated by the onset of auricular fibrillation, myocardial infarction, lobar pneumonia and other severe conditions, it is wise to expedite diuresis by the use of diuretics.

Organic Mercurials: Among the many diuretics available the organic mercurials are considered the most potent, most dependable, and most rapid in action.

The depressant effect of mercury upon the function of the tubular cells promotes the excretion of water by means of osmotic diuresis in the distal tubule. It is debatable whether the main effect consists of blocking the reabsorption of chloride or sodium. At any rate the rejection of the electrolyte enhances the excretion of water. The advantage of organic mercurials over inorganic compounds lies in the fact that they are largely and rapidly excreted by the kidney. Their low dissociability permits control of the degree to which renal reabsorptive capacity is reduced. It is believed that their activity is due to the inhibition of the SH-activated enzyme system presumably by the formation of mercaptides. Strong evidence for this is the fact that certain mercaptans can prevent systemic mercury poisoning and the diuretic effect of the organic mercurials. Dimercaprol (B.A.L.), a dithiol analogue of glycerol, is the most effective of the mercaptans and is used to treat acute mercurial poisoning

In planning a rational diuretic regime with mercurials one should bear in mind their many possible side effects. These reactions can be divided into three major groups: poisoning from either a single excessive dose or accumulative effects; hypersensitivity to either mercury or a specific compound; and the effects of excessive diuresis such as dehydration, electrolyte depletion, or acute urinary retention. The allergic reactions may be prevented by not exceeding 1 cc. in adults and 0.5 cc. in children in the initial test dose. Although deaths and serious side effects rarely occur, the intravenous injection of mercurials should be avoided except in emergencies because of the danger of hypersensitivity and the occasional production of serious arrhythmias, such as ventricular tachycardia, ventricular flutter, and ventricular fibrillation. Dilution and slow infusion do not prevent such reactions The symptoms of *hypersensitivity are usually mild* following the first few injections by any route. They are manifested by a subjective feeling of chilliness, fever, cutaneous eruptions, or vomiting. With subsequent injections more severe symptoms may occur and can ter-

minate in irreversible shock and death. Since hypersensitivity is usually limited to one specific compound, it is best to change preparations at the appearance of any of these reactions. An extremely rare allergic manifestation is agranulocytosis.

Most of the organic mercurial preparations commercially available contain about 40 mg. of mercury and 30 to 50 mg. of theophylline per cc. Table I lists some of the better known forms. The usual site for injection is intramuscular.

Mercaptomerin sodium, U.S.P. (thiomerin sodium) is the only one which does not contain theophylline. The linkage of the mercury ion to sulfur results in comparatively little dissociation locally and the resultant tissue reaction is minimal For this reason it has been recommended for subcutaneous injection. However, when given by this route, the incidence of local reactions such as pain, ecchymosis, and fibrous nodules is about twenty per cent.[2,3] As this compound also has a higher incidence of sensitivity reactions than the other preparations, it is not recommended for routine use.

Merethoxylline procaine, N.N.R. (dicurin procaine) is also available for deep subcutaneous injection, but preferably by the intramuscular route. The drug should not be given to patients sensitive to procaine.

The oral route of administration has been given extensive trial in the last decade. Unfortunately absorption is erratic and the diuretic effect is uncertain. Frequently the symptoms of mercurialism appear. These symptoms are gingivitis, metallic taste, epigastric distress, nausea, abdominal griping, and colitis. Chlormerodrin and mercumatilin are effective in daily doses ranging from one to four tablets. About five to ten per cent of the ingested mercury is absorbed from the intestinal tract. Oral administration of mercurials is not recommended for routine use.

Suppositories of organic mercurials are available, however the absorption is unpredictable and rectal irritation occurs frequently. This route is not recommended.

The usual procedure is to start with an intramuscular test dose of 0.5 cc. of one of the preparations. The injection should be given in the morning or at least six hours before retiring to prevent interference with sleep If renal function is normal and no allergic symptoms or signs appear, the patient may be started on either a course of 1 cc. daily or 2 cc. every other day. Such a regime will prevent excessive accumulation of mercury in the tubules or excessive diuresis which may cause electrolyte imbalance. The patient should be weighed daily or at least every other day. The goal is to achieve and maintain the "basal weight level" rather than actual "dry weight," which is the point where diuretics are no longer effective and when the patient is dehydrated. When the "basal weight level" has been achieved, the injections of mercurials are gradually spaced out in the hope that eventually they will become unnecessary. In patients who are already partially or fully digitalized excessive diuresis is particularly undesirable as it may precipitate hypokalemia, thereby increasing the toxicity of digitalis. "Redigitalization" by the mobilization of cardiac glycosides from the extracellular fluid does not occur. Recent studies[4] have shown that

there is very little digitalis in such fluid space and that the toxic effects are associated with a low potassium plasma level. In patients with marked edema who are expected to require prolonged mercurial treatment, the serum levels of sodium, potassium, chloride, CO_2 combining power, and urea nitrogen are determined at the outset.

Ammonium Chloride: Often the acidifying salt, NH_4Cl, is employed therapeutically to enhance the effect of the organic mercurials.

The mechanism of the diuretic action of NH_4Cl is based upon the increase of the chloride concentration of the extracellular fluid as the cation, NH_4^+ is converted to urea and the replaced anion, HCO_3^-, rapidly goes to CO_2 and H_2O. An appreciable amount of the augmented chloride load to the tubules escapes reabsorption along with a cation, predominantly sodium but also potassium, and an isosmotic quantity of water. The resulting net loss in extracellular fluid promotes the mobilization of edema fluid.

As a result of the acidosis produced, the renal defense calls for the excretion of chloride unaccompanied by fixed cation. The kidney accomplishes this by elaborating ammonia, secreting H^+ for Na^+ and thereby excreting Cl^- in combination with NH_4^+. Full compensation is achieved in three to four days at which time the renal excretion of ammonium chloride may equal that ingested.

Clinically, therefore, ammonium chloride is effective for a period of only one to two days. As the drug may cause gastric irritation, gelatin capsules are administered orally. Enteric coated capsules are absorbed erratically. The usual dosage is 8.0 to 12 Gm. daily, given in divided doses for one to three days, the organic mercurial being administered on the second day. In order to abolish the renal defense pattern, three to four days should elapse between courses of ammonium chloride.

Xanthines: Since the introduction of the potent organic mercurial diuretics, other milder diuretics have been almost completely abandoned Aminophylline (theophylline with ethylenediamine) is employed occasionally. The diuretic effect is produced by an effect upon the renal tubules similar to that induced by mercurials. There is also a brief increase in renal blood flow. It should be remembered that xanthines do more than produce diuresis. They stimulate respiration by lowering the threshold of the respiratory center to pCO_2. Other effects are central nervous system stimulation, increased cardiac work, and smooth muscle relaxation as manifested by bronchodilatation and peripheral vasodilatation.

Orally the various xanthines differ in potency. Theophylline is the most potent. Theobromine is slightly less potent but acts longer. Caffeine is the weakest diuretic and has a more pronounced effect upon the central nervous system. Oral absorption produces very low blood levels. Rectal administration (suppositories) is slightly more effective. The intravenous route achieves very high blood levels and clinical effectiveness. The gastrointestinal irritation produced by oral administration in large doses prevents an effective blood level.

Aminophylline (theophylline ethylenediamine), U.S.P. is the most widely employed soluble theophylline salt. It consists of a combination of

approximately 78 per cent anhydrous theophylline and 12 per cent ethylenediamine. It may be given orally, intramuscularly, intravenously, and rectally. In acute pulmonary edema, despite the report of rare deaths, (presumably due to myocardial stimulation and/or excessive peripheral vasodilatation), it may be administered intravenously if well diluted and given over a period of ten to fifteen minutes. The usual dose is 250 to 500 mg. The blood level and presumably the clinical effect decreases about ten per cent every thirty minutes when given intravenously. *To prevent nocturnal dyspnea, it may be given rectally in the form of a 500 mg. suppository.* Orally it may be given in plain and enteric-coated tablets, 100 to 200 mg. three to four times daily.

Other preparations that may be given are theobromine which is only given orally and choline theophyllinate (choledyl®) which has been introduced very recently. The latter differs from other theophylline preparations in that it is a true salt rather than an addition product. Oral absorption is greater and more rapid than with other theophylline preparations. Gastrointestinal irritation is claimed to be greatly reduced. The recommended oral dose is 100 to 200 mg. four times daily. Daily doses up to 1500 mg. have been reported to be well tolerated.

Carbonic Anhydrase Inhibition: A new and different type of drug has been added recently to the list of diuretics. Acetazolamide (diamox®) produces diuresis by interference with the catalytic effect of carbonic anhydrase in the renal tubules upon the reversible reaction between CO_2 and H_2O:



$$CO_2 + H_2O \rightleftarrows H.HCO_3$$

As the important renal functions for conserving fixed cation depend upon the exchange of H^+ in the renal tubular cell with Na^+ in the tubular urine, and as the source of H^+ is believed to be carbonic acid, it can be readily appreciated that, when the rate of formation of carbonic acid is depressed (by the inhibition of carbonic anhydrase), H^+ and Na^+ exchange in the tubule is greatly reduced. Bicarbonate reabsorption becomes incomplete; titratable acid and ammonia disappear from the urine; and an increased volume of alkaline urine is excreted without significant loss of chloride, phosphate, and the accompanying cations. A metabolic acidosis develops. Other renal transport mechanisms remain unaltered.

If a single daily dose between 250-500 mg. is administered, the peak effect is reached within two hours; 70-90 per cent is excreted unchanged in the urine; and the effect lasts six to twelve hours. A dose lower than 250 mg. orally is ineffective and the ceiling dose is 500 mg. During the subsequent twelve to eighteen hours renal compensation restores the extracellular fluid to a normal level.

The present recommended schedule is to administer 250-500 mg. once daily for three to four days with a rest period of similar duration. Toxic reactions are few. Agranulocytosis has been reported. The early appearance of paresthesias may disappear with continued administration. Acetazolamide may be given with mercurials, each drug being given on alternate days.

Restriction of Sodium Ingestion. *Diets:* In recent years with the growing understanding of the quantitatively reduced sodium excretion in patients with congestive failure and the resultant accumulation of salt and fluid in the body, sodium restricted diets have become very popular. Such diets are most satisfactory with intelligent and cooperative patients. To be effective the restriction must limit the intake of sodium to between 400 and 500 mg. per day. In some patients the sodium intake must be reduced to 150 to 200 mg. Such a restricted diet, unless supplemented with special protein preparations low in sodium, will cause a marked reduction in protein intake. There is still some divergence of opinion whether such a reduction is desirable. The problem needs further investigation. In moderate congestive failure the more liberal sodium intake of 400 to 500 mg. is usually sufficient. When sodium ingestion is severely restricted the use of mercurials can lead to dangerous electrolyte imbalance.

The essential data necessary for planning a sodium restricted diet are the degree of sodium restriction desired, other needed dietary alterations, and the normal food habits and customs of the patient. As these diets can be obtained in any well run hospital or from such sources as the National Academy of Sciences,[5] details will not be presented here. Several points, however, should be emphasized. The sodium content listed for foods is not always exact. The label should always be read. The statement that no salt has been added does not mean that the food itself is free of sodium. In order to permit dietary control by serial estimations of urinary chloride excretion, salt substitutes should not be used. The preparation of food for this diet need not be complicated, but the cook at home or in the hospital should exercise ingenuity in developing flavorings other than salt. There are many flavoring aids that do not contribute significant amounts of sodium to the diet and may be used as desired. Experimentation is essential in order to learn the correct amounts of flavoring. In general it should be remembered that "a little goes a long way!" It is a simple matter to cook all meats and vegetables without adding salt. A small amount of sugar added to vegetables during the cooking period helps to bring out the natural flavor of the food. Fortunately many foods are now processed and packed without added salt or with reduced sodium content.

It should be appreciated that there is a considerable amount of sodium in the water supply of some areas Similarly, water softened by certain ion exchange systems is also high in sodium content. Sodium bearing medicinals, such as the bicarbonate based "antacids" or "alkalizing" preparations may be a problem. Other medicinals containing sodium are certain saline cathartics, barbiturates, sulfonamides, antibiotics, salicylates, and bromides. Certain barbiturates are available which contain calcium rather than sodium. Toothpastes and powders may contain considerable sodium. Detergent residues on kitchenware and dishes may be a further source of adventitious sodium ingestion but if ordinary care is exercised, such residues are not important.

In planning a sodium restricted diet the patient should have good motivation, adequate instructions relating to the need for the diet, and sufficient information concerning its limitations. This is the responsibility of

the physician and should not be delegated to others. The patient should not be led to expect immediate or dramatic results and should know that improvement usually requires many weeks and even months of strict adherence to the diet. In fact group discussions among patients on a low salt diet will provide incentive as well as useful information. Encouragement by all those who come in contact with the patient is very important.

Cation Exchange Resins: Shortly after Segal and associates[6] introduced anion exchange resins as gastric antacids, Dock[7] found that cation exchange resins could prevent the intestinal absorption and promote the fecal excretion of sodium. The mechanism of action is complex[8] and is not discussed in detail here. The affinity of cations for the cation exchange resins, which usually contain H^+ or NH_4^+ in combination with the acidic groups, depends upon the relative concentration of cation and the "exchange capacity" as well as the particular affinity for any one cation. The divalent ions Ca^{++} and Mg^{++} have a greater affinity for the cation exchange resins than do the monovalent cations K^+, NH_4^+ and Na^+, arranged in the order of decreasing affinity.

In practice, the foregoing is important clinically in that a greater exchange with K^+ than Na^+ can occur in the neutral or alkaline intestinal tract particularly when sodium intake is restricted about fifty per cent. The fecal elimination of sodium is decreased as its intake is decreased. There may be a slow loss of calcium if the resins are given continuously.

With increased fecal excretion of fixed cation and increased absorption of H^+, renal compensation is achieved quickly by the excretion of a highly acid urine containing large amounts of NH_4^+ and Cl^-. The hypochloremic acidosis, thus brought about, is soon lost with continuous medication although some degree of hypochloremia may persist and enhance the diuretic effect of organic mercurials. Finally, a large dose administered to patients with normal renal function or a normal dose given to patients with impaired renal function can produce renal decompensation.

In order to avoid severe disturbances in electrolyte metabolism, it has become the practice to employ mixed resins. Carbacrylamine resins, N.N.R. (carbo-resin) is a mixture of 87.5 per cent polyacrylic carboxylic acid resin for cation exchange and 12.5 per cent polyamine-methylene resin for anion exchange. Two-thirds of the cation exchanger contains H^+; one-third K^+. Each gram of resin will remove 1 mEq. (23 mg.) of Na^+ if the patient is on a daily diet of at least 3.7 Gm. of sodium chloride. Initially 16 Gm. are taken orally three times daily between meals. No more than 24 Gm. is advisable for a single dose. When it is necessary to prescribe more than 72 Gm. per day, the number of doses should be increased. To absorb this bulk of medicine, flavored preparations have been concocted to permit suspension of the resin in a glass of water. Many recipes have been devised for incorporating the finely powdered resins in a wide variety of foods.

Untoward effects from resin administration consist of mild acidosis during the first few days (if renal function is adequate), hypocalcemia, and gastric irritation. In the prolonged administration of mixed resins, calcium should be given, preferably at bedtime, to avoid interference from the ac-

tion of the resin ingested during the day. Finally, diarrhea may develop occasionally and fecal impactions of resin may occur on rare occasions in elderly patients.

Since most patients prefer a low sodium diet alone to resin therapy, the practical usefulness of cation exchange resins seems to be limited to those cases of congestive failure where low sodium diets and mercurials are no longer effective. The resins also seem a useful tool to enhance the effects of mercurial diuretics. However, ammonium chloride is much more effective in this respect.

Quinidine: Congestive heart failure may be often associated with arrhythmias which impose an added burden to existing myocardial disease. The most common of these arrhythmias are auricular fibrillation and auricular flutter. Less common precipitants of congestive failure are ventricular, nodal, and paroxysmal auricular tachycardias. It is wiser to treat the congestive failure with digitalis, diuretics, and restricted activities before considering conversion of the arrhythmia to a normal sinus mechanism. *This principle is particularly true in auricular fibrillation and* flutter. In these conditions the ventricular rate will accelerate during the *conversion, unless the AV node is protected by therapeutic dosage of* digitalis.

It has been shown experimentally and clinically that a normal sinus rhythm between sixty and eighty-five beats per minute not only produces a more efficient heart beat but also a higher cardiac output than is found in auricular fibrillation or auricular flutter. The rates associated with auricular, nodal, and ventricular tachycardias of between 120 to 200 beats per minute are obviously much less efficient than a normal sinus rhythm at a normal rate. Another factor to be considered is that in a high percentage of patients, long standing auricular fibrillation with the formation of thrombi in the right and left atria poses a threat of lesser and greater circulation embolism. These embolic phenomena are unpredictable and may be catastrophic. Recent articles[9] suggest that the danger of embolism from conversion is about one seventh that of allowing auricular fibrillation to continue.

Each case must be judged individually as to the merits or demerits of attempted conversion to normal sinus rhythm. Some of the factors to be taken into consideration are (1) the existing mental status of the patient, (2) the duration of fibrillation, (3) the type and severity of heart disease, (4) the ability of digitalis to control the ventricular rate in auricular fibrillation, (5) the cooperation of the patient and family, and (6) the amount of quinidine necessary to maintain normal sinus rhythm once conversion has occurred. Some authorities feel that in auricular fibrillation without congestive failure in which the rate can be controlled easily by digitalis, conversion should not be attempted The usual reasons cited are that (1) some patients with auricular fibrillation when converted to normal sinus rhythm present heart rates greater than 100, (2) there is a high incidence of embolic phenomena during or shortly subsequent to conversion to a normal sinus rhythm, and (3) the administration of quinidine may cause death in a few instances. In the last decade there has been a

general trend toward more active attempts at conversion to normal rhythm, particularly in auricular fibrillation. Although no hard and fast rules have been set up, a few physicians feel safer if anticoagulants are given a week or ten days prior to attempted conversion in order to minimize embolic phenomena. Those who have had extensive experience feel that the incidence of embolism during conversion is negligible and that prophylactic anticoagulant therapy is rarely necessary. Conversion to *normal rhythm and the maintenance thereof is about 100 per cent* effective in people without apparent heart disease; about 90 to 95 per cent effective in those with mild to moderate arteriosclerotic heart disease, and just under 50 per cent effective in those with severe arteriosclerotic heart disease and moderate rheumatic or syphilitic valvular disease. In some "hopeless" cases brilliant results have been obtained.

The generally accepted plan for conversion from auricular fibrillation to a normal sinus *rhythm is as follows: After explaining* the definite but small risk to the patient, the patient is fully digitalized. A test dose of quinidine, 100 to 200 mg. is given orally the day before conversion is attempted. The next day 200 mg. may be given orally every two hours for five doses with a careful check of the pulse, blood pressure, and ECG tracings. It is not usually necessary to take an ECG tracing until just before the fourth dose to check for intramyocardial conduction delay and for other quinidine effects. The next day 300 mg. can be given every two hours for five doses on a similar schedule, and on the third day of attempted conversion 400 mg. may be given on the same schedule.*

Another dosage schedule is to give on the first day 200 mg. at 10 A.M., 300 mg. at 2 P.M., and 400 mg. at 6 P.M., again examining before each dose for pulse, blood pressure, and ECG evidence of intoxication. The next day the initial dose can be 500 mg. with a similar 100 mg. increase per dose. This dosage may be increased until the last individual dose in a day reaches 1.0 to 1.5 Gm. Another method is to give 200 to 600 mg. three to four times daily for several days. A peak blood level is achieved within three to four days if the same dose is given daily.

Once the rhythm has been regularized, one should give 200 to 800 mg three times daily for two to three weeks depending upon the dosage at the time of conversion, and then slowly drop the dosage staircasewise in the hope that 200 mg. given two to four times daily will maintain normal sinus rhythm. In some instances the patient will be unable to be maintained on these schedules. In others the symptoms of "cinchonism" may prohibit conversion. In such patients the use of long term anticoagulant therapy to lessen the dangers of thromboembolism should be considered very seriously.

The appearance of *ventricular tachycardia* in a patient with severe myocardial disease may warrant the use of quinidine intravenously. In such cases the drug should be well-diluted; given very slowly intravenously;

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* [illegible] ...ed for several days [illegible] ...ve days The danger [illegible] are given daily, 30

monitored by serial ECG tracings; and stopped immediately if there is a severe drop in blood pressure, ECG evidence of toxicity such as prolongation of the QRS and QT intervals, or evidence that there is no auricular pacemaker present. In the last instance continued quinidine administration will cause cardiac arrest. Quinidine is the drug of choice for therapy of all supraventricular arrhythmias. Procaine amide (pronestyl) appears to be equally effective in the correction of ventricular arrhythmias. However several cases of agranulocytosis from procaine amide have been reported.

Relief of Pain: In patients with acute congestive heart failure or in those with Cheyne-Stokes respiration the judicious employment of morphine sulfate in doses of 15 to 30 mg. (¼ to ½ grain) will rapidly relieve the discomfort. In acute pulmonary edema the injection of two-thirds of this dose intravenously rather than subcutaneously may be life-saving Morphine does not relieve Cheyne-Stokes breathing but does make the patient less aware of it.

Surgical Procedures: In a few selected patients where the primary disease can be removed or corrected by surgery, such a procedure is the treatment of choice. *Congestive failure must be treated before attempting* surgery. At present surgery is most successful in the following conditions: arteriovenous fistulas, hyperthyroidism, stenosis of the mitral and aortic valves unaccompanied by a significant degree of insufficiency, most cases of constrictive pericarditis, severe pericardial adhesions, and coarctation of the aorta. The morbidity and mortality from surgical procedures in a patient with heart disease are not to be regarded lightly despite the magnificent progress in these procedures. Certainly no patient should be subjected to surgery in whom there are no signs or symptoms of definite and progressive heart failure.

Miscellaneous Forms of Therapy. *Southey Tubes:* Southey tubes have been used for a long time for draining edematous legs. At present the tubes have been replaced by the use of No 20 gauge needles. The procedure is to infiltrate the skin with 1 per cent procaine and then make multiple incisions with the needle. Such a procedure is rarely used now except in the more severe forms of congestive failure when other treatments have failed Similarly, subcutaneous punctures may be made in the edematous scrotum. There will be a significant protein and electrolyte loss from paracentesis and thoracentesis. Mobilization of edema fluid from the tissues accompanied by diuresis does not cause significant protein loss

Genitourinary Problems. In the patient with prostatism, diuresis may not be successful due to obstruction at the bladder neck. An indwelling catheter may be used during the diuresis if the bladder is partially decompensated. The catheter should be withdrawn as soon as possible to avoid introducing ascending infection and chronic bladder irritation. During the period of catheterization, sulfisoxale (gantrisin®) may be employed to minimize urinary infection. The recommended oral dose is 0.5 to 1 0 Gm. three times daily. Fluids need not be forced and toxicity is low. Later a transurethral resection may be of great benefit if the patient's condition permit.

Phlebotomy: Phlebotomies have been used for many years for acute pulmonary edema. The rationale has been that the sudden reduction in venous pressure will relieve the backward failure of the heart. More recently bloodless phlebotomy has been recommended either by rotating tourniquets or an apparatus that automatically produces a venous pressure sufficient to prevent return to the heart, but low enough not to prevent arterial inflow into the limb. It is the writer's opinion that such procedures are rarely, if ever, necessary and are dangerous for several reasons. (1) Actual phlebotomy, unless the patient is phlethoric may further increase an anemia that is already embarrassing the myocardium, (2) tourniquets inadvertently have been left attached more than ten or fifteen minutes resulting in some permanent ischemia and in several instances actual amputations have been required, (3) acute pulmonary edema responds in the vast majority of patients to oxygen and morphine alone, and (4) such procedures are alarming and painful to the patient. Further agitation and stimulation to the sympathetic nervous system aggravate the condition.

Production of Hypothyroidism: Blumgart has been recommending for many years the production of hypothyroidism in the euthyroid patient with intractable congestive heart failure to lessen cardiac work. The original procedure was total or subtotal removal of the thyroid. With the advent of goitrogenic drugs, propylthiouracil was tried. More recently I_{131} has proven to be the drug or tool of choice.

The patient's basal metabolic rate is determined by use of iodine uptake, BMR and/or the plasma bound iodine level. I_{131} is then given in three or four well-spaced small doses. A single dose is more apt to produce a marked thyroiditis with the concomitant release of thyroxine and temporary hypermetabolism. The metabolic rate and blood cholesterol are checked at intervals to determine the amount of hypothyroidism produced. The effects do not appear for several weeks. The final low metabolic rate may not be reached for three or four months. Mild to moderate relief of symptoms is achieved in a little under fifty per cent of cases If the dose of radioactive iodine is too high, myxedema is produced. This usually aggravates and exaggerates the symptoms of congestive failure. The myxedema can be relieved easily by daily administration of small doses of desiccated thyroid extract. Although the results are not as striking as in the relief of intractable angina, this form of medication is well worth trying in certain carefully selected patients.

Prevention and Treatment of Complicating Factors: The physician should be acutely aware of the possibility of certain complications. The primary conditions that may produce congestive heart failure are surgically remediable conditions such as stenotic mitral and/or aortic valves, the tetralogy of Fallot, ventricular and atrial septal defects, patent ductus arteriosus, coarctation of the aorta, arteriovenous fistulas, certain other congenital anomalies, and constrictive pericarditis.

Primary or complicating factors that can be treated medically include severe anemias, hyperthyroidism, hypoproteinemia, hypothyroidism, vitamin B complex deficiency as manifested by beriberi heart disease, and

thromboembolism. It has been well demonstrated that hemoglobin levels below 12 Gm. decrease efficiency and work output. Primary pernicious anemia can produce congestive heart failure when the hemoglobin level drops to 4 or 5 Gm. In this condition the use of liver extract and vitamin B_{12} is much more important than digitalis, salt restriction, or diuretics. Although a low serum albumen per se will not cause congestive heart failure, any finding significantly below 4 mg. per cent will enhance the accumulation of extracellular fluid. A liberal protein intake and, in emergencies, salt free albumen injections will correct this disorder. Hyperthyroidism occurs in about five per cent of patients with auricular fibrillation. In hyperthyroidism accompanied by auricular fibrillation and congestive failure, digitalis and diuretics may be unnecessary once normal metabolism has been reestablished. Hypothyroidism with a high blood cholesterol level is often associated with coronary arteriosclerosis and myocardial damage. The judiciously slow administration of thyroid extract should be employed. This will prevent the precipitation of angina and myocardial infarction. The ventricular hypertrophy and dilatation thought to accompany myxedema is in most instances due to pericardial effusion, and will disappear during thyroid medication. Beriberi disease is a thiamine chloride deficiency which produces congestive failure because of interference with intracellular enzyme activities. The patient in chronic congestive heart failure often has subclinical nutritional deficiencies including avitaminosis due to the anorexic effects of dyspnea, orthopnea and splanchnic congestion. Prophylactically the patient should be given vitamin supplements and as liberal a protein diet as possible.

The danger of thromboembolism in congestive failure is higher than previously suspected. The venous stasis in the legs and pelvis due to edema and restricted activity may cause unsuspected thromboses and recurrent pulmonary emboli. Such complications easily may be overlooked and considered part of the primary disease. It has been claimed that thirty-five per cent of the patients with heart disease have thrombi in the left atrium or left ventricle and that sixty-five per cent of patients with myocardial infarction have postmortem evidence of thromboembolism. Although these figures may be too high, the serious implications cannot be ignored.

In rheumatic heart disease and particularly that associated with auricular fibrillation there is a very high incidence of thrombi in the left atrium. Such thrombi may produce recurrent cerebral embolism. The acute type of embolism simulates a primary cerebral vascular accident The slow type may appear to be a progressive organic brain disease It is due to a slow fragmentation of the thrombus. It has recently been demonstrated that four per cent of institutionalized patients with organic brain damage have multiple embolic infarcts.[10] In such cases thrombi may not be identifiable at autopsy. As a result, today's clinician must think very seriously of long term anticoagulant therapy in chronic congestive failure, particularly in those patients who have a past history of myocardial infarction.[11] It remains to be demonstrated just how much protection can be provided by such therapy.

Obstructive and infectious diseases of the urinary tract may aggravate the renal factor in congestive heart failure. Routine renal function tests should always be done. When prostatism is suspected the residual urine after voiding should be measured. If there is a residual of more than 30 cc. (1 ounce) the bladder size should be watched carefully during diuresis. A catheter should be inserted if voiding becomes difficult. Urinary infection should be treated vigorously by a five day course of sulfisoxazole (gantrisin®) or some similar drug. If the infection is not eliminated, urine culture should be done and appropriate broad spectrum antibiotic therapy instituted.

Finally, hepatic hypoglycemia with confusion and coma has recently been described in congestive heart failure.[12] Often this cannot be correlated with the apparent clinical degree of liver impairment. As the manifestations of hypoglycemia are nonspecific and may be confused with other causes of disordered behavior, the real nature of the hypoglycemic episodes may not be recognized immediately. If the observer is aware of its potential occurrence in any circumstance in which liver function is impaired, though perhaps unobtrusively, this condition can be corrected easily and rapidly by the administration of 50 cc. of 50 per cent glucose intravenously. It is very important to recognize and treat hypoglycemia as soon as possible in order to prevent irreversible cerebral damage. It is wise to withdraw some blood for a sugar determination just before the injection of glucose.

Hazards in the Treatment of Congestive Heart Failure. ***Iatrogenic Electrolyte Imbalance:*** With the development recently of important means of exploring and influencing human ionic equilibrium and with the ever increasing employment of the principle of salt restriction, iatrogenic salt depletion in its various forms has become more evident and much more frequent in the last fifteen or twenty years.

In congestive failure the main therapeutic measures which contribute to salt depletion are (1) the mechanical removal of large volumes of salt-containing fluids by thoracentesis, paracentesis, Southey tubes, and continuous gastric or intestinal suction without parallel administration of saline, (2) stringent salt restriction, (3) energetic mercurial diuresis, (4) prolonged exchange resin therapy, (5) sudden relief of severe urinary retention, (6) prolonged use of ammonium chloride and similar salts, and (7) broad spectrum antibiotic therapy complicated by diarrhea medicamentosa.

Salt depletion occurs more often when several of these factors are employed simultaneously, and particularly in the patient with congestive failure who is being treated with dietary sodium restriction, mercurial diuretics and ammonium chloride. The use of exchange resins and diamox® further complicates the situation. The various syndromes produced are described below.

The Low Salt Syndrome: The low salt syndrome is characterized by a decrease in plasma sodium and chloride concentration, acidosis, a decrease in urinary chlorides, and an increase in blood urea. The clinical manifestations are weakness, drowsiness, muscular cramps, thirst unrelieved by

water, anorexia, nausea, vomiting, decrease in urinary output, and refractoriness to diuretics. When salt depletion is severe, fluid retention will be enhanced. Other clinical signs consist of restlessness, mental confusion, a fall in blood pressure, increased pulse rate, and the full blown picture of shock and coma.

In mild cases this syndrome may be treated by giving salt orally either in soups or in sugar-coated tablets. In more severe cases salt must be given intravenously, usually in a five per cent solution. Not more than 200 cc. should be administered at one time and should be given slowly. A total of *400 cc. should not be exceeded in a twenty-four hour period.*

There are several methods to calculate how much sodium is required to achieve the normal extracellular level. It has been found that often only one-third or one-half of a calculated dose is needed. For this reason a calculated dose should be administered in divided portions and by frequent estimations of the serum electrolytes. One method of estimating the theoretical amount required is based on the calculation that fifty-three per cent of body weight is total body water as in the following example.

A man weighing 70 kilograms has about 37 kilograms of total body water. If his serum sodium is 122 mEq./liter, then his total deficit of sodium is 142 minus 122 = 20 x 37 = 740 mEq. As 1 Gm. of sodium chloride contains 17.1 mEq. of sodium, then 100 cc. of five per cent salt solution contains 17.1 x 5 = 85.5 mEq. This patient will therefore require 740 divided by 85.5 x 100 = approx. 860 cc. of five per cent salt.

Hypertonic salt frequently causes disagreeable side effects such as intolerable thirst and thrombophlebitis. In a number of cases the energetic use of five per cent salt has resulted in a downward course accompanied by increasing edema.

Hypochloremic Alkalosis: This condition is more common than the low salt syndrome. It is most often produced by mercurial diuresis due to the proportionately greater elimination of chloride than of sodium. Sodium remains at near normal levels while the serum chloride concentration decreases. It may be avoided if injections of mercurials are spaced a few days apart, and if ammonium chloride is administered concurrently. Alkalosis develops with an increased bicarbonate level and urea retention. A concomitant decline in serum potassium often occurs. Milder cases may be given 3 to 6 Gm. of ammonium chloride orally in solution or in gelatin capsules. When the condition is acute, a one per cent solution of ammonium chloride in five per cent glucose should be given slowly at not more than 200 cc. per hour and in a daily dose not exceeding 1000 to 1500 cc. as only 10 to 15 Gm. of ammonium chloride can be detoxified in the normal liver by conversion to urea in twenty-four hours. Most cases of congestive heart failure have some degree of liver insufficiency. If ammonium chloride cannot be tolerated, 20 cc. of the ten per cent acid, dilute hydrochloric acid, may be mixed in 600 to 1000 cc. of water and given with meals in divided doses.

Chronic Dilution Hyponatremia: Chronic dilution hyponatremia may develop gradually in some patients with untreated congestive heart failure and in others receiving relatively conservative treatment. As there is usu-

ally a hypernatremia and total increase in body sodium in congestive heart failure this condition implies associated renal tubular dysfunction. The patient should be fully digitalized and *not* given hypertonic saline. The appearance of this syndrome at best implies a grave prognosis.

Hyperchloremic Acidosis: Hyperchloremic acidosis occurs most frequently in patients with impaired renal function. Hyponatremia may coexist as well as hypokalemia. This syndrome usually occurs in patients being treated energetically by the use of organic mercurials and constant ammonium chloride administration. It may also occur as a result of the predominant removal of cation by resins. Intermittent use of the resins or ammonium chloride with mercurial diuresis will help to avoid this complication.

Hypokalemia: Hypokalemia may result from the excretion of potassium during mercurial diuresis when dietary sodium is restricted. It may also *result from absorption of potassium by the resins and is only partly offset* by the use of potassium-containing resins. Potassium depletion should be avoided in congestive heart failure as it enhances digitalis toxicity. Clinically the symptoms of hypokalemia are weakness, malaise, tachycardia, shallow respiration, stupor, the so-called "fish-mouth" expression, and muscular paralysis. The electrocardiogram may be helpful diagnostically. When available frequent determination of serum potassium levels are indicated. When hypokalemia is associated with hypochloremic alkalosis, potassium chloride is the drug of choice. In acidotic states potassium citrate or acetate are indicated. The daily oral dose is 3 to 6 Gm. which must be regulated by determinations of serum potassium levels.

Hypocalcemia: Hypocalcemia may develop from the prolonged use of both the sulfonic forms of the cationic exchangers and the carboxylic resins. Because of the frequently associated hypokalemia and acidosis, clinical tetany rarely occurs.

Bedrest: The hazards of absolute bedrest have become more apparent in the last few decades. The rigid restriction of patients to bed not only will produce muscular weakness and psychological changes, but may also favor the development of thromboembolism.

Oxygen: Although oxygen is very useful in the treatment of acute congestive failure, it becomes dangerous when administered continuously for long periods. The most serious complication is bronchial irritation leading inexorably to pulmonary edema and death. This may occur in normal individuals or in animals when mixtures containing more than sixty-five per cent oxygen are administered for more than twenty-four hours. 70 to 100 per cent oxygen should be given intermittently and for only six hours at a time. The inhalation of pure oxygen favors the development of atelectasis by washing out nitrogen from the pulmonary alveoli. In cor pulmonale chronic anoxia and severe carbon dioxide retention are present. The sudden introduction of oxygen inhalation, where the main stimulation of respiration is the chemoreceptor drive, may depress respiration to such an extent that carbon dioxide retention is markedly increased. As the tension of CO_2 rises in the blood, its narcotic action produces drowsiness, confusional psychoses, coma, and death.

Xanthines: Xanthines not only induce diuresis but cause central nervous system stimulation, bronchodilatation and the relaxation of smooth muscle anywhere in the body. The two dangers of aminophylline therapy are its myocardial stimulating properties in a patient whose myocardium is severely damaged and the collapse or even death from peripheral vasodilatation that may occur during rapid injection.

Ammonium Chloride: Although the action of ammonium chloride as a diuretic is most helpful in enhancing mercurial diuresis, and in the prevention of excessively low blood chloride levels, it may be very dangerous in patients with impaired renal function. A significant rise of blood urea level may occur. Although this is not established as necessarily harmful, the administration of a large dose such as 15 Gm. a day to patients with normal renal function or smaller amounts to patients with renal insufficiency will lead to the accumulation in the blood of ammonia in concentrations toxic to brain tissue. Psychoses and coma may appear. In addition *the acidosis produced by ammonium chloride ingestion may depress carbohydrate utilization.* This may complicate the management of patients with diabetes.

Organic Mercurials: Mercurial diuretics may easily produce hypochloremia and the low salt syndrome. Muscle cramps, confusion, stupor, or a shocklike state may occur in patients on restricted sodium diets. In addition a significant amount of other cations such as potassium and calcium may be carried off during mercurial diuresis. Potassium loss induces or accentuates digitalis intoxication. Mercurial poisoning can occur in those patients given mercury orally. Excessive injections can cause renal tubular damage. Intravenous administration may cause sudden death. Finally, severe allergic reactions can occur.

Dietary Restriction: The increasing use of very low salt diets makes it imperative to avoid nutritional deficiencies, particularly in proteins and the vitamin B complex. Use of the Karell diet imposes additional deficiencies of calories, iron, and vitamins A, C, and thiamin. Patients who require frequent mercurial diuresis should not be allowed to restrict their salt intake excessively. Such restriction is best reserved for those who can be kept free of edema without mercurials.

Ion Exchange Resins: Although the use of ion exchange resins is not widespread it should be remembered that these agents can produce chronic potassium and calcium depletion. The chief hazard is sodium depletion. Gastrointestinal upset and acidosis may be caused by the ammonium chloride contained in some resins.

Morphine: Although morphine is strikingly beneficial in acute congestive failure, particularly pulmonary edema, it may cause untoward effects in some patients. The most serious effect is depression of respiration, particularly in cor pulmonale. Other effects are constipation, vomiting, cutaneous itching, impairment of bladder function in prostatism, and hypotension in elderly patients. Hypotension is produced by marked peripheral vasodilatation. It may well precipitate collapse in severely ill patients who are maintained in the upright position.

TABLE I

Generic Name (Trade Name)	*Organic Mercurial Content (mg /cc)*	*Mercury Equivalent (mg /cc)*	*Single Dose*	*Route*	*Marketed*
Meralluride U.S P. (Mercuhydrin)	130	39	1–2 cc	I.M.	1–2 cc. ampules 10 cc vials
Mercurophylline Sodium, U S.P. (Mercuzanthine)	135 100	38 28	1–2 cc. 1–2 tablets daily	I.M. Oral	1–2 cc. ampules Tablets
Mersalyl and Theophylline, U S P. (Salyrgan-Theophylline)	150 120	39.6 32	1–2 cc. 1 tablet daily	I M. Oral	1–2 cc. ampules Tablets
Mercumatilin, N.N R. (Cumertilin)	132 67	39 20	1–2 cc. 1–4 tablets daily	I.M. Oral	1–2 cc. ampules Tablets
Mercaptomerin-Sodium, U S P... (Thiomerin Sodium)	130	43	1–2 cc.	I.M.	1.4 and 4.2 Gm. vials made with 10 or 30 cc. of sterile water, respectively. Also requires refrigeration. Discard if turbid.
Merethoxylline Procaine, N.N R.. (Dicurin Procaine)	100	39 3	1–2 cc.	I.M. or deep s.c.	10 cc. vials containing 50 mg. per cc Theophylline 45 mg. per cc. Procaine base.
Chlormerodrin, N N R .. (Neohydrin)	18 3	10	1–4 tablets daily	Oral	Tablets

Digitalis: Complications from digitalis therapy are becoming increasingly frequent. This is due to rapid digitalization with the purified glycosides, hypokalemia from the energetic use of diuretics, and lack of recognition of some of the more unusual forms of digitalis intoxication. The physician should be aware of toxic manifestations such as diarrhea, visual disturbances, Stokes-Adams attacks, the sudden appearance of nodal tachycardia in a patient with auricular fibrillation, and a change from normal sinus rhythm to auricular fibrillation and atrial tachycardia. Finally it should be remembered that some patients can gradually become dedigitalized and may develop symptoms of congestive failure. Redigitalization should be attempted cautiously before other preparations or therapy is instituted.

Phlebotomy: The production of phlebotomy either by withdrawal of blood or by decreasing the venous return from the limbs by means of tourniquets helps to relieve pulmonary congestion and edema. The beneficial results are often outweighed by the deleterious effects. Phlebotomy may increase a pre-existing anemia, the use of tourniquets may precipitate shock, and also fever from impaired heat dispersal. Respiratory activity may suddenly be increased shortly after tourniquets are released by the introduction into the circulation of large amounts of lactic acid and carbon dioxide accumulated during the period of stasis. The discomfort of tourniquets may cause anxiety and restlessness. Finally, if tourniquets are left on too long ischemia and gangrene may ensue.

SUMMARY

The management of congestive heart failure requires accurate diagnosis, adequate but not too energetic treatment, and the prevention and removal of conditions which complicate the existing heart failure

As congestive heart failure is primarily due to myocardial disease and secondarily due to the retention of salt and water in the tissues, the prime requisite in the management of this condition is restoration of cardiac function to as near normal as possible. In the milder forms of congestive failure restriction of activities and slow digitalization will accomplish this goal. In the moderate forms of congestive failure restricted activity without absolute bedrest, digitalization, and accompanying mercurial diuresis will soon restore the patient to normal activities. In acute congestive failure accompanied by pulmonary edema, heroic measures may be necessary. These include the judicious use of morphine and oxygen When a fast ventricular rate due to auricular fibrillation is present, the use of a quick acting cardiac glycoside may be lifesaving.

In the long term management of patients with congestive heart failure adequate digitalization must be achieved and maintained If this is not sufficient to prevent accumulation of fluid, there are two alternatives. The first is the use of intermittent organic mercurial diuretics accompanied by short courses of ammonium chloride. The second is the use of a moderately restricted sodium chloride intake with diets containing 400 to 500 mg. of sodium per day. The use of both mercurials and a low salt diet concomi-

tantly is risky. It is imperative to guard against electrolyte depletion by intermittent estimations of the plasma levels of sodium, potassium, chloride, and bicarbonate. The long term use of anticoagulants may prevent thromboembolism. In about fifty per cent of cases with intractable and severe congestive failure, the production of hypothyroidism will produce beneficial results.

It is important to search for and remove any primary disorder that may cause congestive failure such as a surgically remediable condition, hyperthyroidism, and thiamine deficiency. Nutritional deficiencies, anemias, and urinary disorders should be corrected.

The physician must be aware of the dangers and toxic manifestations associated with the powerful drugs available for the treatment of congestive heart failure. Such drugs include morphine, oxygen, digitalis, organic mercurials, xanthines, resins, ammonium chloride, and anticoagulants.

Finally, the physician must be willing to accept responsibility for the adjustment of the patient to his environment. A balance must be struck between overoptimism and overzealous restriction of the patient's activities. The patient with congestive heart failure now may live many years, and it is the duty of the physician to see that these years are productive and happy ones.

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MORRIS W. STROUD, 3RD, M.D.

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Digitalis

Introduction: Digitalis has been employed as a therapeutic agent for centuries, but it was not until 1785 that its value in "dropsy" was *first recorded by Withering. Its true place as a therapeutic agent in* congestive heart failure and certain cardiac arrhythmias has only been established in the last sixty years. The intent of this chapter is to emphasize the basic principles underlying the clinical use of the digitalis and *digitalis-like agents. To do so, the historical background,* chemistry, and physiologic and pharmacologic action of the glycosides are presented as a background to their clinical usefulness and potential toxicity.

Historical Background:[5] The cardiac glycosides contained in a large number of plants have been used by primitive people for centuries for killing game with poisoned arrows and by ingestion for tribal ordeals. Below are listed chronologically some of the important milestones in the medical aspects of these glycosides

Ca 1500 B C.	Squill was mentioned as a medicine in the Ebers Papyrus.
300 B C. – 476 A.D	The Romans employed squill as a diuretic, heart tonic, emetic, and rat poison.
1250 A D.	Digitalis (foxglove) was mentioned in the writings of Welsh physicians and was used internally or locally for a number of unrelated diseases ranging from epilepsy to skin ulcers
1242	Digitalis purpurea was described by Fuchsius, the word digitalis deriving from the resemblance of the flower to a human digit.
1775–1785	The English physician and botanist, William Withering, recognized that digitalis was the active agent in a remedy consisting of twenty or more different herbs. After a ten year trial he published his famous account which set forth excellent rules for digitalis administration that went for the most part unheeded for over a century
1799	John Ferriar seems to have been the first to realize that the primary action of digitalis was upon the heart; the diuretic effect a secondary one
1890	Sir Thomas Fraser discovered the digitalis-like action of strophanthus while studying African arrow poisons.
1911	Sir James Mackenzie felt that the principal therapeutic effect of digitalis was the slowing of the ventricular rate

ment in the steroid ring system, and the absolute necessity of an unsaturated butyro lactone ring at C 17.

Semisynthetic derivatives have been made by reaction of aglycones with various substances. As yet such compounds have not been made in sufficient quantity for clinical use. An exception is acetylstrophanthidin which is prepared by esterification with acetic acid *via* OH at C 3. It differs from strophanthus glycosides in being fairly well absorbed orally. It has been recommended as a tool to measure clinically the amount of "digitalization."

Distribution and Fate of Digitalis:[1,2,5] A good deal of factual knowledge concerning the distribution and fate of the cardiac glycosides in the human body has been accumulated from the three methods presently employed. These consist of (1) observation of the subjective and objective effects of different preparations in different amounts, (2) observation of randomly-labelled digitoxin obtained by the biosynthetic method of growing digitalis plants in an atmosphere containing C^{14}, and (3) bioassay of various fluids and tissues by the very sensitive embryonic duck heart method.

TABLE 1

BOTANICAL SOURCES AND MAJOR CHEMICAL COMPONENTS OF CARDIAC GLYCOSIDES OF CLINICAL IMPORTANCE

	Plant Source	*Precursor Glycoside*	*Split Off by Enzymatic and Mild Alkaline Hydrolysis**	*Glycoside*	*Split Off by Acid Hydrolysis**	*Aglycone or Genin*
Digitalis	*D purpurea* (leaf)	purpurea-glycoside A (desacetyl-digilanid A)	glucose	digitoxin	digitoxose (3)	digitoxigenin
		purpurea-glycoside B (desacetyl-diglanid B)	glucose	gitoxin	digitoxose (3)	gitoxigenin
		—	—	gitalin	digitoxose (2)	gitaligenin (gitoxigenin hydrate)
	D lanata (leaf)	lanatoside A (diglanid A)	glucose + acetic acid	digitoxin	digitoxose (3)	digitoxigenin
		lanatoside B (diglanid B)	glucose + acetic acid	gitoxin	digitoxose (3)	gitoxigenin
		lanatoside C (diglanid C; cedilanid)	glucose + acetic acid	digoxin	digitoxose (3)	digoxigenin
Strophanthus	*S Kombé* (seed)	K-strophanthoside	glucose	K-strophanthin-β (strophanthin)	glucose + cymarose	strophanthidin
		K-strophanthoside	glucose (2)	cymarin	cymarose	strophanthidin
		K-strophanthin-β	glucose	cymarin	cymarose	strophanthidin
		—	—	cymarol	cymarose	strophanthidol
	S gratus (seed)	—	—	ouabain (G-strophanthin)	rhamnose	ouabagenin (G-strophanthidin)
Scilla (Squill)	*Urginea maritima* or *indica* (bulb)	scillaren A	glucose	proscillaridin A	rhamnose	scillaridin A

*One mol of sugar or acetic acid is split off, unless the number of mols is otherwise indicated in parentheses

From Goodman & Gilman, 2nd Ed p 671

Absorption:[1,2] Oral and rectal absorption of digitalis whole leaf and the purified glycosides is consistent and unaffected by moderate to severe intestinal disease. On the other hand, strophanthus and squill are absorbed poorly and erratically. Subcutaneous and intramuscular absorption is somewhat erratic, usually painful, and may produce sterile abscesses. Intravenous absorption is uniform and effective for all of the purified glycosides.

A comparison of the oral and intravenous dose of a cardiac glycoside preparation that must be given to achieve similar effects in patients suffering from combined atrial fibrillation and congestive failure reveal the following:

$$\% \text{ absorption} = \frac{\text{Oral Effect}}{\text{I.V. Effect}} \times 100$$

Glycosides of squill (five to ten per cent), lanatoside-C (ten per cent), digitalis powder and tincture, digilanid and digifolin (twenty per cent), digoxin (twenty to fifty per cent) and digitoxin (100 per cent). Gastrointestinal absorption of the effective dose is usually complete for all the above-mentioned drugs within two hours.

Distribution:[1,2] Once in the blood stream there is a variable time lag before full cardiac effect is achieved. This seems to depend upon the binding by serum albumen. This binding effect does not seem to alter qualitatively the cardiac action. By the bioassay method digitoxin disappears from the blood fairly rapidly, fifty per cent within a few minutes, eighty-five per cent after two hours, while lanatoside-C can no longer be detected in the serum at the end of thirty minutes Very little of the active principles get into extracellular fluid and the recorded digitoxin content of edema fluid has never exceeded 0.2 mg. per liter Therefore, mobilization of edema fluid does not mobilize digitalis enough to be of any clinical significance. The toxic manifestation concomitant with massive mobilization and diuresis of extracellular fluid are presumably due to electrolyte distribution.

Recent experimental work would indicate that digitoxin is not concentrated specifically in cardiac muscle, that it can be easily washed out of the heart, and that it is found in the soluble supernatant intracellular parts of cells, but not in the nuclear and mitochondrial portions. The inference is that the action is at the cell membrane rather than due to specific intracellular changes. Some recent studies suggest that the glycosides may have a specific effect upon the actomysin threads of cardiac muscle.

Elimination and Destruction:[1,2] The actual fate of the cardiac glycosides is unknown. What the metabolic degradation products are and whether they have little or significant biological activity remains to be solved. About all that can be said, at present, is that the liver appears to be involved in the degradation of that fraction of the active glycoside not excreted. At present the radioisotope studies and the bioassay technic give conflicting pictures of the excretion of the digitalis glycosides. Biological assay would indicate, at least for digitoxin, that there is a prolonged excretion (two to four weeks) of about one-half of the active agent while the radioisotope technic shows that within one hour seventy-four per cent of the labelled digitoxin is already in the molecules of degradation products. Summing up, not more than 0.05 mg. of digitoxin per day is rendered

ineffective, but a good deal of the persistent effectiveness may well reside in unknown degradation products.

Actions of Digitalis. ***Fundamental Actions:***[5] The fundamental action of digitalis is its ability to increase the force and speed of myocardial contraction. Since Vulpian first noted this effect upon the frog's heart in 1855, many investigators, including Cushny in 1897, have contributed to the literature on this subject. More recently, to mention a few specific investigators, Cattell and Gold (1938), Kabat and Visscher (1939), and Wedd and Blair (1948) have shown conclusively that digitalis acts directly on heart muscle to increase the force of systolic contraction independently of other cardiac or extracardiac factors. In addition, the ventricle empties more completely and the relative length of time in each cardiac cycle occupied by systole is shortened. These changes make for better diastolic filling and a potential increase of coronary flow of thirty per cent. Just how this increased force of systolic contraction is obtained and why after digitalis the heart seems able to do a given amount of work with less consumption of oxygen (Gremels, 1933; Peters and Visscher, 1936) is unknown at present.

The second most important effect of digitalis upon the heart in man is its action upon the rate and conduction of impulses through the heart. At present it is felt that receptors in the heart and elsewhere are "sensitized" by digitalis resulting in an increased vagal tone with a relative decrease in sympathomimetic tone. In early digitalization this effect is mediated through the vagus and can be blocked by atropine, exercise, or cooling of the vagal nerves. In full digitalization as will be explained later, these actions are presumably mediated through the direct effect of digitalis upon the conduction system in the heart and cannot be blocked to any great extent by the agents just mentioned. From the foregoing discussion one would feel that digitalis actually can improve the normal heart and exert a significant effect upon the heart rate and conduction of the specialized neuromuscular system of the normal heart. That this is far from true can be easily explained. The human heart under normal conditions is operating at maximum efficiency. If we consider the left ventricle as the primary pump and the right ventricle as an outpouching that in most instances is passively following the action of the left ventricle and if we consider the left ventricle to operate as a symmetrical sphere, it can be easily deduced on theoretical premises that the heart operates mechanically within the correct boundaries for optimal efficiency in contraction and relaxation. In the normal heart any increased force of contraction and increased emptying produced by digitalis brings the heart into a relatively inefficient range and actually prevents optimum filling under conditions of stress. On the other hand, in the heart in congestive failure which is dilated beyond the normal range and in which the actual stroke volume is small and the systolic contraction relatively feeble, digitalis by its unique action returns the heart to within normal limits for systolic and diastolic areas.

The effect of the administration of digitalis to the normal person as far as the vagus and intrinsic conduction system of the heart is concerned, produces little action upon the pacemaker (SA node) or the specialized conduction tissue within the therapeutic dosage range. On the other hand

if the heart is in congestive failure, there is a reflex slowing of the pacemaker brought about by the improved stroke volume, general circulation, and tissue oxygenation. In the cardiac arrhythmias in which digitalis is of help, effects of little importance for the normal heart become much more apparent. To cite one example, the effect of digitalis on the conduction of the A-V node in the normal heart is insignificant while in the heart in atrial fibrillation where conduction through the A-V node is of the utmost importance, the effect is exaggerated as the ventricular rate is markedly slowed out of all proportion to the expected effect. Of course, other factors are important, such as the relief of congestive failure which in turn would tend to slow the ventricular rate. The writer feels that digitalis must also have some unique action upon cardiac muscle that prevents excessive ventricular filling in the failing heart and subnormal filling in the normal heart. If such a concept could be proven it would be most helpful. Unfortunately there is no experimental evidence to back up this theory. At present the evidence is in the other direction!

Collateral Circulatory Effects:[5] As outlined in the historical background of digitalis, observers have thought for many years that most of the *changes in congestive heart failure could be explained by actions occurring* outside of the heart. The most recent claims which have been adequately refuted by more detailed investigations were that the primary action of digitalis was to lower venamotor tone and pressure. The action of digitalis was likened to an acute phlebotomy and supporting evidence was produced experimentally indicating that a certain amount of blood could be trapped upon the administration of digitalis in the dog's liver and splanchnic area. In careful studies such as those of Harvey, Richards, Ferrer, and Cournand, and their respective coworkers, it has been demonstrated conclusively in combined left and right ventricular failure that the increased cardiac output due to stimulation of the myocardium occurs *before* any measurable changes in central venous pressure and that there is no relation between the magnitude of fall in venous pressure and the degree of increase in cardiac output. Similar studies in patients with isolated left ventricular decompensation showed that with digitalization there is a significant increase in stroke volume and cardiac output accompanied by a decrease in pulmonary arterial pressure. These changes are achieved without alterations in right ventricle end-diastolic pressure and could not be ascribed to the action of the drug on systemic venous pressure (Harvey, 1949).

As to the effect of digitalis on the vascular flow in the specialized beds of the various organ systems, there is no indication that digitalis has any direct effect. Any increase or decrease in flow through cerebral, renal or other special vascular beds may be considered at least for the present to be secondary to systemic changes produced by the direct effect upon the myocardium.

Effects on Special Systems and Organs: For a long time it was felt that digitalis had a direct diuretic effect upon the kidneys. However, digitalis is not an effective diuretic in the absence of congestive heart failure with the possible exception of noncardiac edema states associated with the presence of excessive circulating adrenal corticosteroids. Increased renal venous pressure (usually found in congestive heart failure) decreases so-

dium excretion and urine outflow. The improved circulation induced by digitalis may lower the obnormally high renal venous pressure and thereby enhance diuresis. Summing up, it may be stated that the increased diuresis following the administration of digitalis in congestive heart failure is secondary to the improvement of the action of the failing heart, but that there is some indication that a slight but significant effect on diuresis does occur in the normal individual perhaps by competing with some desoxycorticosterone-like hormones in the renal tubular mass. Other unimportant actions are the production occasionally of slight gynocomastia presumably due to the close chemical relationship to the sex hormones. The production of gastrointestinal symptoms by the whole leaf preparations are in part due to direct irritation of gastric mucosa. In toxic doses the effect is central in origin. Finally but very rarely allergic phenomena may arise all of which are described later under the heading of digitalis toxicity.

Relation to Cations:[2] Although it has been known for many years from animal experiments that there was some relationship between digitalis effect and concentration of various cations it has only been recently that renewed interest and clinical investigations have occurred because of the availability of new technics such as the flame photometer. The three important cations involved are sodium, potassium, and calcium. At present there is no clearcut evidence that an excess or deficiency of sodium within the clinical range significantly affects the actions of digitalis upon the heart. However it does so indirectly. For instance, it is well documented that in congestive heart failure the body tends to store sodium excessively. If sodium is severely restricted in a patient's diet, significant diuresis may occur. Conversely, the combined use of a severely restricted sodium intake and mercurials may result in the "low salt syndrome" with all the subjective, objective, and chemical findings listed elsewhere. Such a clinical state impairs renal function and thereby the diuretic effect of digitalis. It has been known for years that calcium has a synergistic action with toxic doses of digitalis, both having a propensity to produce an excessive amount and duration of muscle contraction. Although most texts and articles concerning the clinical use of digitalis quote one report on several sudden fatalities resulting from the intravenous administration of calcium to digitalized patients, it has been the reviewer's impression that such a risk is more theoretical than actual. Of course it would be foolish to administer calcium to a patient already showing toxic symptoms or signs of digitalis poisoning. The cation that has been studied most recently is potassium. Although the serum concentration of potassium may be altered very little in congestive failure, the total body content in its intracellular and/or extracellular distribution may be markedly disturbed. Some potassium deficit of the cardiac muscle not necessarily associated with a low serum level commonly occurs in congestive heart failure. This deficit may be compounded by anoxia, acidosis, inadequate nutrition and many therapeutic procedures such as dietary restrictions, mercurial diuretics, ammonium chloride, resins, and the use of carbonic anhydrase inhibitors. Finally, impaired renal functon, diabetes, and the well known effect of cortisone in enhancing potassium excretion may increase such a deficiency. Although high levels of serum potassium have profound deleterious effects

upon the heart, it is not known whether they have any influence upon the therapeutic action of digitalis. However, it has been well documented that a low serum potassium will increase the toxicity of a given amount of digitalis whether the impairment is induced as mentioned above or withdrawn as by hemodialysis. Digitalis toxicity may be abolished temporarily in man as in animals by the administration of potassium even when the blood level is within normal range. It should be mentioned that potassium ion loss by heart muscle occurs with digitalization, the loss apparently proportionate to the degree of digitalization.

Quantitative Differences in Digitalis Preparations: The quantitative differences between the various preparations of digitalis employed in the treatment of congestive heart failure depend upon their rate and degree of absorption from the gastrointestinal tract, the uniformity in composition or potency of any one preparation, how much the preparation is bound to the plasma, and the rate of decay and elimination of the particular agent. In Fig. 2 may be seen a chart illustrating what an average single dose of representative fast and slow acting glycosides will do. The curves illustrate the marked variation in the time for full effect to be reached and the variability of decline not only among the different preparations but also for the same one. It should be mentioned in passing that the *qualitative* biological effects of the cardioactive glycosides are almost identical. However there still is some controversy on this subject. Some European observers feel that strophanthus and its derivatives exert a relatively greater influence upon the myocardium than upon the Purkinje system. The sudden and sustained popularity of digitoxin around 1940 due to the enthusiasm of Gold and his associates finally provoked an interesting and provocative editorial (Ann. Int. Med.: April, 1954). The editorial pointed out that the very advantages claimed for digitoxin, such as the lack of gastrointestinal upset has been one of the most serious drawbacks to its clinical use. The reason is that there may be little warning of the onset of such toxic conditions as a serious arrhythmia or a drug-induced congestive heart failure. Although much of the toxicity observed in the last fifteen years has resulted from misguided and rigid therapeutic schedules, it is easier to slip unnoticed into toxicity with a purified glycoside such as digitoxin than with the whole leaf preparation in which digitoxin is the main therapeutic agent. Batterman and his associates have claimed that gitalin has a greater margin of safety than other agents. Similar claims have been made in the past for other preparations and at present there is no "proof positive" that any one agent is definitely superior to any other under ideal supervision.

Indications and Contraindications for Digitalis Administration. ***Congestive Heart Failure and Potential Heart Failure:*** The most important use of digitalis is in congestive heart failure. By definition congestive heart failure means impairment of the myocardium with a consequent reduction in the mechanical efficiency of the heart resulting in impending or overt signs described below. In isolated left ventricular failure, dyspnea, orthopnea, and signs of pulmonary congestion develop. With combined left and right ventricular failure there is a marked weight gain, the appearance of peripheral edema to a greater or lesser extent and a congested

painful liver in addition to the pulmonary findings. In isolated right ventricular failure the pulmonary signs and symptoms are absent. Often there is an insensible collection of extracellular fluid before these symptoms and signs of failure appear. In a suspected or known case of congestive heart failure, this can be most easily recognized by frequently weighing the patient. A weight gain of 2.27 to 2.72 kg. (5 to 6 pounds) may occur before the overt signs appear. When congestive failure is not secondary to initial myocardial damage in conditions such as cardiac tamponade, digitalis is not only useless but can be harmful.

The effectiveness of digitalis will vary depending upon how much of the failure is due to direct myocardial disease, valvular obstruction, and whether the myocardial damage is an acute inflammatory or degenerative one. However, digitalis may always be tried if the heart is enlarged and congestive phenomena are present. Similarly where overt signs and symptoms are not present in sufficient number or degree to make a positive diagnosis, a careful trial of digitalis is indicated. In most instances when there is no symptomatic improvement or sign of weight loss after adequate digitalization, the drug should be discontinued. Opinion does differ concerning the value of giving digitalis to a patient with an enlarged heart but in whom failure has never appeared. Such "prophylactic digitalization" recommended by Christian in the 1930's has never been fully accepted.

Cardiac Arrhythmias. 1. *Sinus Tachycardia and Bradycardia:* Digitalis is never indicated in either of these two conditions unless there is definite danger or accompanying signs of the development of congestive heart failure secondary to a persistent tachycardia.

2. *Paroxysmal Atrial (Auricular) Tachycardia:* This arrhythmia unlike simple sinus tachycardia has an abrupt onset and abrupt cessation. It is often induced by sudden emotional stress and may be stopped by simple procedures that stimulate the vagal reflexes. Such measures include carotid sinus massage and painful stimuli. If the attack is prolonged and if signs of heart failure are developing, digitalis is the drug of choice. Digitalis may be given in intravenous form to sensitize the afferent receptors that increase "vagal tone." Within a half hour of injecting a cardiac glycoside such as lanatoside-C (0.4 to 0.8 mg.) the rhythm may revert spontaneously to normal or carotid sinus massage may become effective. Other measures are available such as the use of parasympathomimetic drugs or drugs that induce similar vagal reflex by their baroreceptor effect induced by the elevation of arterial blood pressure. However such drugs may be contraindicated. There is the potential danger of inducing cardiac standstill, ventricular fibrillation and death by the use of parasympathomimetic drugs. The introduction of hypertension by sympathomimetic drugs may overwhelm a diseased heart. Carotid sinus massage is not an innocuous procedure in elderly people, as it may cause syncope or convulsions. It has been known to precipitate cerebral vascular thrombosis in rare instances.

3. *Ectopic Atrial or Ventricular Systoles:* Digitalis *per se* will not abolish ectopic atrial or ventricular systoles. However impending congestive failure, particularly in rheumatic valvular disease, may be heralded by the onset of ectopic atrial beats. In such instances digitalizaton may abolish the aberrant focus by improving the nutrition and oxygenation of the

atrium and by relieving the increased atrial pressure caused by the failing left ventricle. Theoretically the same may hold true for ectopic ventricular beats, but in actual practice digitalis is rarely indicated. In fact, ectopic ventricular beats in an otherwise normal heart usually can be abolished by exercise or by eliminating stimulants such as tobacco and coffee. It should be remembered that the appearance of ectopic ventricular beats during digitalis administration are often the first signs of intoxication.

4. *Atrial Flutter:*[4] Atrial flutter is a disorder of atrial activity characterized by rapid regular abnormal contractions ranging from 220 to 400 per minute initiated by an ectopic pacemaker. Very rarely can the A-V node conduct all such impulses. The usual arrhythmia consists of an auricular rate of around 300 per minute followed by a ventricular response of 150 per minute (2:1 block). Unless the heart is essentially normal and there are no signs or symptoms of impending or actual congestive heart failure, digitalis is the drug of choice. If direct conversion of the abnormal rhythm to a normal sinus rhythm is attempted with quinidine, a sequence of events occurs which is potentially dangerous to the diseased heart. Quinidine will slow the ectopic pacemaker and at the same time improve conduction through the A-V node. Before the ectopic focus is abolished, a 1:1 response may occur at rates around 180 to 220. This sudden acceleration of ventricular rate has occasionally caused acute cardiac failure and sudden death. The routine use of digitalis will prevent this. Digitalis will impair A-V node conduction and the ventricular rate will slow as the 2.1 block increases variably to 3:1 and 4:1. Finally, the arrhythmia changes to auricular fibrillation with a ventricular rate well below 100 which is not influenced significantly by exercise or atropine.

In most instances a conversion from atrial flutter to atrial fibrillation occurs in the therapeutic range of digitalis dosage. As soon as it occurs the digitalis dosage can be dropped to a maintenance one. At this point, if indicated, quinidine may be administered with full assurance that the ventricular rate will not rise significantly as the A-V conduction is impaired by both a reflex vagal and direct effect upon the A-V node. Occasionally it will be found that the administration of digitalis will cause a direct conversion to normal rhythm. It can be assumed that in this event atrial flutter was induced by dilatation of the atria, anoxia, and impaired circulation. Digitalis relieved this condition by improving the stroke efficiency, restoring normal circulation and thereby eliminating the ectopic atrial pacemaker. There is no good evidence that digitalis administration prior to attempted conversion to normal rhythm by quinidine will lessen the chances of success.

5. *Atrial Fibrillation:*[4] Briefly, atrial (auricular) fibrillation is a cardiac arrhythmia in which the rate of the ectopic atrial pacemaker(s) exceeds the ability of the atrial muscle to follow in an orderly fashion. Electrically and physically the atrial muscle responds in a chaotic, disorganized fashion as manifested both by the "f" waves which replace the P wave in the ECG and by the "bag of worms" recorded by high speed motion pictures during direct visualization at surgery or experimentally. The "f" waves beat irregularly against the A-V node. As a result the "irregular, irregular" ventricular response varies between 140 to 180 beats per minute in the

absence of any impairment of A-V node conduction. In the presence of pre-existing impairment of A-V node conduction the ventricular rate may be much slower (60 to 140 beats per minute).

The principles for the use of digitalis in atrial fibrillation are essentially the same as those for atrial flutter. In an otherwise normal heart paroxysmal atrial fibrillation can be treated by quinidine without prior digitalization. Where there is a history and/or physical findings suggestive of organic heart disease, digitalization should be accomplished before any attempted conversion to normal sinus rhythm. The conversion of atrial fibrillation to normal sinus rhythm by quinidine can be shown to go through an intermediate stage of atrial flutter in most instances if continuous ECG tracings are taken. Therefore, the same dangers are present for the diseased heart as described in the previous paragraph for atrial flutter (Q.V.). Digitalis tends to perpetuate the atrial fibrillation and at the same time slow the ventricular rate by its vagal and direct action upon the A-V node. Full digitalization is not accomplished until a significant direct effect upon the A-V node is indicated by the poor response of the ventricle to moderate exercise or atropinization. The usual clinical picture is a completely irregular ventricular rate between 140 and 170 per minute with occasional ectopic ventricular beats which are due to the poor circulation and anoxia. These ectopic ventricular beats are *not* a contraindication to digitalis therapy. As the ventricular rate is slowed they will tend to disappear.

The ventricular response to digitalization is much more striking when congestive heart failure accompanies the arrhythmia because of the combined effects of digitalis upon the A-V node and upon the failing left ventricle. In rare instances digitalization will directly convert the atrial disorder to normal rhythm presumably for the same reason given for atrial flutter. Hyperthyroidism should always be considered as an etiological factor in the production of atrial fibrillation, although the incidence is probably less than five per cent. There are two reasons for this: (1) Experimental work has shown that digitalis may cause myocardial damage when administered to drug-induced hyperthyroid animals. In actual practice this theoretical possibility may be ignored. (2) Control of the ventricular rate in the presence of hyperthyroidism by digitalis is less efficient.

6. *Partial and Complete Heart Block:* In first degree heart block where the P-R interval is lengthened as an indication of impaired conduction by the A-V node or in second degree heart block where there is A-V conduction block with occasional dropped ventricular beats, digitalis is not indicated. Rather an attempt should be made to improve conduction of the A-V node by the use of sympathomimetic agents to decrease any vagal component. However, in a supraventricular rhythm varying with third degree heart block, (complete dissociation between the atria and the ventricles), digitalis may be the drug of choice when other drugs have failed to reconvert and maintain sinus rhythm. The main reason for this is occurrence in one form of the Stokes-Adams syndrome in which periods of unconsciousness sometimes accompanied by convulsions may occur because of an asystolic period during the transition to an idioventricular rhythm. Digitalization may cause and maintain complete heart block by its known paralyzing effect upon the A-V node and thereby prevent such

occurrences. There is a common clinical impression that digitalis should not be used in the presence of complete heart block. The stated reason is that administration of digitalis may slow the heart rate further causing more circulatory failure. In actual practice if latent or overt congestive heart failure is present, digitalis should be used as outlined previously for congestive heart failure and potential failure.

7. *Ventricular Tachycardia:* Paroxysmal ventricular tachycardia is rarely an indication for digitalis. In fact the presence of such an arrhythmia suggests the possibility of digitalis toxicity. Other measures should be energetically employed before digitalis is considered. For the sake of completeness it should be mentioned that in a few instances digitalis has been reported effective after all other forms of therapy were exhausted. Presumably the administration of digitalis relieved congestive heart failure and thereby abolished the ectopic ventricular pacemaker. Such instances are rare and other accepted measures should be tried first.

7a. ***Coronary Insufficiency and Myocardial Infarction:*** In coronary insufficiency (angina pectoris) without congestive heart failure, digitalis seldom proves of benefit. Occasionally the administration of digitalis to patients with an advanced degree of coronary atherosclerosis may increase the symptoms. In the average case it is unlikely that digitalis will change the symptoms as the effects upon coronary circulation and cardiac work are insignificant. When congestive heart failure is present, digitalis administration is indicated but should be given with caution as such patients presumably are particularly susceptible to ventricular fibrillation. Occasionally not only the dyspnea but also the pain may be relieved. In acute coronary occlusion accompanied by myocardial infarction, digitalis is not indicated unless the indications noted previously are present, such as auricular fibrillation and congestive failure. In these cases digitalis should be administered with extreme caution and constant supervision. Theoretically the increased force of myocardial contraction, the more complete ventricular emptying and the increased velocity of blood circulation might induce embolic phenomena arising from thromboses in the heart chambers or peripheral vessels. The use of anticoagulants should reduce this potential hazard.

7b. ***Conditions Not Primarily of Cardiac Origin:*** (1) Anemia and Polycythemia. Digitalis is of no value in these conditions. If indications of congestive heart failure persist after the primary disorder is treated adequately, digitalis should be tried.

(2) Hypo- and Hyperthyroidism. In hypothyroidism or myxedema congestive phenomena may occur. The "dilated" heart noted on physical and x-ray examination has been shown to be due to a pericardial effusion rather than an actual dilatation of the heart chambers. Digitalis is not indicated in this condition. Some form of thyroid should be given. In hyperthyroidism agents that will lower the basal metabolic rate are indicated. Digitalis may be used if atrial fibrillation and congestive heart failure are present with the note that the hyperthyroid heart is more susceptible to digitalis toxicity than the normal one.

(3) Nutritional Deficiencies: In beriberi of advanced degree with extensive edema, cardiac enlargement, and pronounced dyspnea, the parenteral

administration of vitamin B_1 in large doses causes the disappearance of the abnormal clinical features. In actual practice latent thiamin and other B complex deficiencies may occur in patients with prolonged heart failure due to a poor dietary intake. In consequence, adequate vitamin administration using the whole B complex as well as thiamin is indicated. In these nutritional disorders with congestive failure the heart is probably functioning reasonably well and in actuality there is a high cardiac output. Digitalis is of no benefit as the fault is basically a blockade in carbohydrate utilization with pyruvate accumulation.

(4) Nephritis: Acute glomerulonephritis or the nephrotic syndrome may produce a condition sometimes hard to distinguish from congestive heart failure. Unless it can be proven that cardiac failure is also a factor in the production of the edema, digitalis is contraindicated.

(5) Pulmonary Disease: In advanced pulmonary disease, whether primarily of the lungs or of the pulmonary blood vessels, right-sided heart failure may occur (cor pulmonale) eventually accompanied by congestive phenomena. Although the results are not as striking in this type of failure as in either acute left-sided or combined left and right-sided failure, digitalis should be tried. The results are variable. If digitalization produces no change or if the symptoms and signs of failure increase or are not changed by digitalization, the drug should be discontinued. Other measures such as phlebotomy, bronchodilators, and antibiotics should be considered.

(6) Pregnancy: Pregnancy places a temporary load upon both the normal and abnormal heart. There is absolutely no indication for the use of digitalis in a patient with a normal heart who has been adequately observed from the first trimester. False signs of congestive failure in the last trimester are due to the increased blood volume, pressure of the near-term baby upon the pelvic vessels and upward displacement of the diaphragm. On the other hand pregnancy in a woman with chronic heart disease requires careful evaluation throughout the pregnancy. As pregnant women with organic heart disease have a death rate twice that of pregnant women without heart trouble, everything should be done to lessen this heavy toll. The same rules apply in pregnancy for the use of digitalis as in congestive heart failure and the arrhythmias. Prophylactic digitalization prior to delivery may well be indicated in the most severe cases. The subject is adequately covered elsewhere in this volume.

ADMINISTRATION OF DIGITALIS

(a) Official Preparations.
(b) 8 criteria of acceptance.
(c) Guides to safe digitalization.
(d) Fast and Slow digitalization.

Administration of Digitalis Preparations:[1,2,3,5] To administer the cardiac [illegible] pertly requires a good deal more knowledge, [illegible] of the patient than do other forms of ther- [illegible] w what conditions to treat, what to expect

from treatment and what can be expected of each type of preparation. He must have some knowledge of prior digitalization, be able to differentiate the signs and symptoms of congestive heart failure from those of digitalis intoxication, and be able to not only diagnose the arrhythmias amenable to digitalis therapy, but also to be on the alert to avoid adding further digitalis to a digitalis-induced arrhythmia. The indications for digitalization and the signs and symptoms of digitalis intoxication are covered in other sections of this chapter. This section deals mainly with the different digitalis preparations and the general rules for their administration.

Before discussing the administration of the cardiac glycosides, it is most important to have a clear cut picture of the various preparations available, their dosage range and some idea of the onset and duration of biological activity. Only the official digitalis preparations are covered in this section. Following are listed such preparations and also illustrative tables (II & III). Fig. 2 also illustrates the different rates of biological absorption and excretion.

DIGITALIS PURPUREA PREPARATIONS[5]

1. Digitalis tablet, U.S.P. This preparation is usually available in 0.1 Gm. tablets but can also be obtained in a powder, injection, and tincture. It is prepared from the dried leaves of digitalis purpurea and contains 0.2 to 0.4 per cent digitoxin plus digitonin, digitalin, antirhinic acid, digitalosun, digitoflavone, inisitol, and pectin. The biological assay of the whole leaf preparation is based upon measurement of the lethal dose in pigeons. Each commercial sample must be assayed against a standard (U.S.P. digitalis reference). One U.S.P. unit is defined as 0.1 Gm of reference standard. The present standard is U.S P. XI and is approximately thirty per cent stronger than the U.S.P. X prior to 1936 when the whole leaf was assayed in cats against the U.S.P. unit

1-a. Digalen, N.N.R. This preparation contains in the amorphous state the natural mixture of cardiac glycosides of the whole leaf separated from the inert substances. It is standardized exactly as the Digitalis tablet, U.S.P. Although it may be given orally in liquid or tablet form, its main usefulness is that it can be given intravenously when oral whole leaf medication is contraindicated. It is available as a sterile solution in ampules (0 5 U.S.P. unit per ml.). Thus 2 ml. is roughly equivalent to 0.1 Gm. of the powdered whole leaf.

1-b. Digifolin, N.N.R. Exactly the same as digalen.

2. Digitoxin tablet, U.S.P. It is derived from a natural glycoside of digitalis purpurea by the removal of glucose. The commercial preparation is usually a mixture of cardioactive glycosides. The purity must be at least ninety-five per cent and strength within twenty per cent of the U.S P. reference standard. As gitoxin is measured as digitoxin in this chemical assay, commercial samples of digitoxin U.S.P. have been found to contain varied but appreciable amounts of gitoxin which have relatively little biologic cardioactivity. Therefore, there may be a wide variation in the biologic activity of the various commercial digitoxin preparations. A few of the various trade names include digitoxin, digitaline nativelle, unidigen, purodigen, and digisidin.

3. Gitalin (amorphous) N.N.R. This preparation is also known as gitaligin. It is a mixture of amorphous glycosides obtained from digitalis purpurea. The drug is assayed biologically by the U.S.P. method for digitalis. It was formerly known as verodigin N.F.

DIGITALIS LANATA PREPARATIONS[5]

1. Digilanid, N.N.R. This preparation is a mixture of the amorphous crystallized lanatosides-A, B and C obtained from digitalis lanata leaves. Proportions are as they naturally occur, forty-seven per cent A, sixteen per cent B, and thirty-seven per cent C. Its actions are almost identical to the official digitalis leaf and it is assayed gravimetrically.

2. Lanatoside-A. There are no commercial preparations for this glycoside, but digitoxin and acetyl digitoxin are derived from it, the first by removal of glucose and acetyl while the latter is derived by removal of glucose but not of acetyl.

3. Lanatoside-B. No commercial preparation is available.

4. Lanatoside-C. U.S.P. Its potency is obtained by pigeon bioassay and may legally vary from 85 to 120 per cent of the lanatoside-C reference standard It is marketed only for oral administration and usually contains 0 5 milligrams of the glycoside.

5. Deslanoside (deacetyl-lanotoside-C) U.S.P. is derived from lanatoside-C by alkaline hydrolysis. The loss of the acetyl group makes the glycoside more soluble and more stable than its precursor. Otherwise its actions are identical. It is assayed colorimetrically against the standard preparation. It is marketed in two and four milliliter ampules, each milliliter containing 0.2 milligrams of drug for intramuscular or intravenous use.

6 Digoxin, U.S.P. Digoxin is pharmacologically similar to lanatoside-C and is derived from it by removal of glucose and acetyl groups. It contains between 90 to 110 per cent of labelled contents and is assayed colorimetrically, the reference material being a standard digoxin.

STROPHANTHUS AND OUABAO PREPARATIONS[5]

1. Ouabain (G-strophanthin) U.S.P. It is a sterile aqueous solution for injection, each ml. of which contains 0.25 or 0.5 mg. of drug. It is a pure glycoside but must be bioassayed by the official digitalis method (pigeons); a standard ouabain preparation being employed as a reference material. It is for intravenous use only and is obtained from the seeds of *Strophanthus gratus* or from the wood of *Acocantheria schimperi* (ouabao tree).

2. Strophanthin, N.F. Like ouabain it is prepared only for intravenous injection; each ml. usually contains 0.3 or 0.6 mg. of strophanthin. It is either a glycoside (K-strophanthin-B) or a mixture of glycosides obtained from the strophanthus Kombe. After assay it is standardized to half the potency, per milligram, of ouabain U.S.P., K-strophanthoside, a natural glycoside isolated from the mixture.

3. Acetyl strophanthidin. It is a synthetic elaboration of the aglucone strophanthidin. It is biologically assayed in cat units against a reference standard. 0.5 mg. of the drug is approximately three cat units equivalent to 0.3 Gm. of powdered whole dry purpurea leaf.

SQUILL PREPARATIONS[5]

1. Scillaren, N.N.R. Urginea maritima ("sea onion") contains two natural glycosides, component A and component B, in the proportion of about two parts of A to one part of B. Scillaren is a purified, stable, chemically standardized preparation containing A and B in the same proportions as occur naturally. The drug is assayed gravimetrically and is available only for oral administration in tablet form (0.8 mg.) and in solution (0.8 mg./ml.).

2. Scillaren-B, N.N.R. This preparation consists of the amorphous component B. It is for intravenous use and is marketed in 1 ml. ampules containing 0.5 mg. of the drug.

3. Urginin, N.N.R. This preparation is similar to Scillaren except the components A and B are in equal portions. It is marketed as oral tablets containing 0.5 mg. of the drug. It is assayed gravimetrically as are all the squills as well as by the U.S.P. method for digitalis.

EIGHT CRITERIA OF ACCEPTANCE[5]

Of the eight criteria of acceptability of the digitalis preparations as listed by Goodman and Gilman, six of the criteria are found equally in all the preparations at present used clinically. These criteria are listed below:

1. Effective myocardial action.
2. Uniformity of potency. (The purified glycosides may be slightly more uniform than the whole leaf preparation)
3. Ease of administration.
4. Drug stability.
5. Adequate intestinal absorption (exception ouabain and strophanthin).
6. Cheapness.
7. Margin of safety (therapeutic: toxic ratio).

In most of the preparations the therapeutic range seems to be two-thirds of the toxic level. Several recent articles suggest that as far as gitalin is concerned the therapeutic level may be about thirty-six per cent of the toxic range. Animal preparations do not bear this out. Final judgment must await further well controlled studies.

RATE OF ACCUMULATION AND ELIMINATION[1,2,3]

Under this heading a clinician has four, possibly five, different rate categories as illustrated in Table 2 and Fig. 2 describing the rapidity of onset of action, the duration of action, and the rate at which the effect decreases.* The fastest acting, acetyl strophanthidin, is of no use as a therapeutic agent *per se* but can be a useful tool in determining rapidly the need for digitalis in doubtful cases. The second group, which consists of ouabain and strophanthin may be used in emergencies for very rapid action, but only intravenously and are not recommended for long term usage. The third group, lanatoside-C, and deslanoside have an action which is almost as rapid in onset as strophanthin and ouabain, but the action may persist for

* In Table III may be found dosage tables for the official digitalis, strophanthus, and squill preparations Such a table emphasizes the need for individualizing the digitalizing oral and intravenous dose and daily oral maintenance dose.

TABLE 2

RAPIDITY OF ONSET AND DURATION OF ACTION OF CARDIAC GLYCOSIDES

Agent	*Route*	*Starts*	*Action Maximal*	*Regresses*	*Gone*
A. Acetyl Strophanthidin	I V.	30 sec.–5 min.	12 min.	30 min	2 hours
B. Strophanthin / Ouabain	I.V.	3–10 min.	½–2 hrs.	8–12 hrs.	1–3 days
C. Lanatoside-C	Oral	30 min.	1–2 hrs.	16–36 hrs.	2–3 days
	I.V.	10 min.	1–2 hrs.	16–36 hrs.	2–3 days
Deslanoside	Oral	30 min.	1–2 hrs.	16–36 hrs.	2–3 days
	I.V.	10 min.	1–2 hrs.	16–36 hrs	2–3 days
D. Gitalin	Oral	60 min.	6–7 hrs.	2–3 days	5–7 days
	I.V.	5–10 min.	6–7 hrs.	2–3 days	5–7 days
Digoxin	Oral	2 hours	4–6 hrs.	2–3 days	4–7 days
	I.V.	½ hour	4–6 hrs	2–3 days	4–7 days
E. Digitoxin	Oral	2 hours	2–9 hrs.	2–3 weeks	3+ weeks
	I.V.	½ hour	2–9 hrs	2–3 weeks	3+ weeks
Digitalis Leaf	Oral	6 hours	12–48 hrs.	1–2 weeks	2–3 weeks

several days. Gitalin and digoxin have a slightly slower onset and a somewhat longer action while the final group of digitoxin and digitalis take about two hours for the onset of action and two to three weeks for termination of any measurable action. Thus at the present time the clinician has cardiac glycosides with action ranging from a fleeting flash-like effect to a stable persistent action of two to three weeks.

One point that may not be evident from the graphs and the description of the drugs should be emphasized. As yet there is no ideal method of standardization of the individual drugs or even batches of the same drug. All the bioassay and gravimetric methods have objectionable features. However, on the whole, the variation between batches of the same drug are minimal and if the following rules of administration are carried out, this objectionable feature becomes more theoretical than real.

GUIDES TO SAFE DIGITALIZATION

1. *Never give the drug without ascertaining whether digitalis has been given previously.* All too often this phase is neglected. The electrocardiogram is not a reliable method for determining the degree of digitalization. A judicious telephone call to the previous physician or hospital is mandatory. If such information is unavailable, digitalis should be administered with extreme caution.

2. In the vast majority of cases rapid digitalization is not only unnecessary, it may be injurious and even lethal. In most instances where digitalis is indicated, such as congestive heart failure, limitation of activity, mild mercurial diuresis, decrease in the excessive salt intake, and other forms of

therapy usually combined to produce enough abatement of symptoms which allow the clinician to slowly digitalize the patient over a period of weeks rather than hours or days. Improvement from the simple restriction of activity in forcing either a bed or a chair existence without any other form of therapy will induce a diuresis and symptomatic improvement that can continue for days.

3. *The cardiac glycosides should never be given by rule of thumb.* Any plan of therapy requires a considered guess of the amount of drug required to produce the desired effect. Although it has been established for digitoxin that a single oral dose of 1.2 mg. will produce definitely beneficial effects with only minor gastrointestinal symptoms, this is rarely a necessary or wise procedure. As listed in the rule above, although previous digitalis medication may have occurred, other factors such as electrolyte imbalance may be unsuspected. If vomiting does occur one is at a loss to know how much of the drug was absorbed and how much was vomited Finally, any of these so-called rule of thumb initial doses if given to enough people can and do cause death.

4. *The therapeutic effect is desired, not the toxic effect.* In most instances this can be achieved. In others the myocardium may be so severely damaged, that digitalization alone will not achieve therapeutic effects without bordering on toxic signs and symptoms. In this event other additional measures must be used.

5. *Tolerance to digitalis does not develop.* So-called "tolerance" is either due to the fact that the maintenance dose is too low or that the underlying condition has worsened. Too often the physician has switched to some other preparation and has ascribed any beneficial effects to the peculiar qualities of that preparation In most instances an increase in the maintenance dose of the initial drug would have produced the same effect.

FAST AND SLOW DIGITALIZATION

Most cardiologists feel that except in a rare emergency the drug of choice is the whole leaf preparation of digitalis The purified glycoside digitoxin at the present time might be slightly more popular. However, it does seem to require more careful supervision than the whole leaf. The main reason is that its toxic effects are not heralded as often by symptoms recognizable to the patient and the physician. Nausea, yellow vision, ectopic ventricular beats, and other symptoms and signs described more fully in the following section usually come on early and often soon enough to safely warn of impending digitalis toxicity when the whole leaf preparation is used. That this is not true with digitoxin has been amply confirmed by many observers over the last fifteen years. It is now known that serious arrhythmias and the reappearance of congestive failure due to overdigitalization can occur with the use of digitoxin with little symptomatic warning.

For the patient who has developed mild congestive failure over a long period of time and who can be re-evaluated weekly, a suggested initial digitalization schedule would be to give 0 3 Gm. daily either in one dose or divided doses for five days and then drop to 0.1 Gm. daily and reobserve at the end of the week. If full effects have not been achieved, the dosage

schedule could then be either 0.2 Gm. daily or an alternating schedule of 0.2 Gm. one day to 0.1 Gm. the next day, with re-evaluation in another week. Such regime could be continued until the desired therapeutic effects or toxic signs or symptoms are manifested. If more rapid digitalization is desired, 0.2 to 0.4 Gm. may be given every six to eight hours for several doses noting the clinical effect before each new dose is given. Thereafter smaller doses may be administered until the desired effect is achieved. In the rare individual in pulmonary edema, cyanotic, and apparently in extremis more urgent digitalization is necessary. The author feels the physician's aim should be to get the patient somewhere between one-half and two-thirds digitalized in a day and "full digitalization" later. This will afford some protection and insure against toxicity. In such a case, one has a choice of either the most rapid acting group—ouabain and strophanthin —or one of the lanatoside preparations. The strophanthin and ouabain preparations have an advantage which is apparently not realized by some clinicians in that the onset of action is slightly faster and the main action is gone in eight to twelve hours, instead of sixteen to thirty-six hours for the lanatoside preparations. This has not only the advantage of getting very rapid action, but it also allows the concomitant administration of longer acting drugs such as the I.V. preparation of the whole leaf or digitoxin, thus minimizing cumulative toxic effects of the two drugs. The use of the rapid acting drug demands very close observation on the part of the clinician in that he must be most careful to avoid toxicity during the concomitant administration of the fast and long-acting drugs. This usually demands reobservation at intervals of two to four hours during the first twenty-four to forty-eight hours. Either strophanthin or ouabain may be employed. The usual recommended dosage schedule is 0.5 mg. intravenously followed by 0.1 to 0.25 mg. every half hour until desired effect is achieved. The lanatoside-C preparations are a bit slower in onset. An initial I.V. dose of 0.8 mg. of cedilanid, digilanid, or digoxin followed by 0.2 to 0.4 mg. every two to four hours will afford some protection. Rarely will such a dosage schedule cause serious toxicity even in the face of previous unsuspected digitalis administration or hypokalemia. The importance of examining a patient as a guide to digitalization cannot be overemphasized. Such observation demands good clinical judgment as to the extent of relief of the manifestations of congestive heart failure. Although venous pressure and circulation time can be utilized, such measures are rarely needed. The main guides to successful therapy are the relief of orthopnea, dyspnea, and nausea symptomatically and the overt signs of diuresis such as the disappearance of rales, shrinking of the liver, and weight loss. The conversion of a gallop rhythm to a normal beat is a good sign. In patients with manifest edema the best guide is probably a daily weight chart at the same time of day with the same amount of clothes or lack of clothing under similar circumstances. In congestive heart failure associated with auricular fibrillation the ventricular rate is helpful. As described in the previous section the maintenance of a ventricular rate (60 to 80/minute) which is not elevated significantly by mild exercise or atropinization indicates that not only the vagal reflex mechanism but the direct effect upon the conduction tissue has been achieved.

TABLE 3

	*Dose for Initial Digitalization**		*Daily Oral Maintenance Dose*
	Oral	*Intravenous*	
1. *Digitalis Purpurea*			
Digitalis, U.S.P. .	1.0- 2 0 Gm.	—	0.05–0 30 Gm.
Digalen (Digifolin) N.N.R.	1 0- 2.0 Gm	1 0–2 0 Gm	0 05–0 30 Gm
Digitoxin, U.S.P. .	1.0- 2 0 mg	1 0–2 0 mg	0 05–0 30 mg.
Gitalin, N.N.R.	4 0- 8 0 mg	—	0 25–0.10 g
2. *Digitalis Lanata*			
Digilanid, N.N.R	3 0- 6 0 mg.	0 8–1 6 mg	0 33–0 66 mg
Lanatoside-C, N.N R.	5 0-10 0 mg	—	0 5 -3.0 mg
Deslanoside, U S P.	—	1 2–1 6 mg.	—
Digoxin	2 0- 4 0 mg	0 8–1 6 mg.	0 25-1.25 mg.
3 *Ouabao and Strophanthus*			
Ouabain, U S P.	—	0 5–1 0 mg	0 6 -1.0 mg
Strophanthin, N F.	—	0 5–1 0 mg.	0 6 -1 0 mg.
Acetyl Strophanthidin	—	0 6–1 2 mg	—
4. *Urginea Maritima*			
Scillaren, N.N.R.	9 6–14 4 mg	—	0 8 -3.2 mg
Scillaren-B, N.N.R.	—	0 5–1 75	—
Urginin, N.N R.	6 0–12 0	—	0 5 -2.0 mg

* Based on a normal weight of 70 kg. (150 lb), no digitalis within three weeks and no electrolyte or similar complications

Another point that should not be overlooked is the intelligence of the patient. An intelligent patient can be forewarned of the symptoms of the impending toxicity and be able to report by telephone if such symptoms develop unexpectedly. Detailed specific instructions both verbally and written are necessary as even the most intelligent patient may overdose himself by misinterpreting the physician's instructions. This may sound obvious but all to frequently this is a cause of over- or underdigitalization.

If either on the initial digitalization or some time during the maintenance of digitalization by the whole leaf, the drug seems to be losing its effect, the maintenance dose can be increased. If toxic symptoms or signs develop before the desired therapeutic effects are reached, one of the glycosides such as gitalin, digoxin, or digitoxin may be tried. Although in most instances no improvement may be noted, occasionally dramatic therapeutic successes occur. As noted in the previous section, gitalin may prove to have a greater margin of safety than the other glycosides.

DIGITALIS TOXICITY[2,3]

Symptoms and Signs. ***Gastrointestinal:*** The commonest toxic manifestations are directed toward the gastrointestinal tract. The most frequent and early complaints are lack of appetite, nausea, and sense of fulness. Often these symptoms are hard to distinguish from the gastrointestinal

discomfort secondary to congestive heart failure. If they occur early in the course of initial digitalization by the whole leaf preparation, local irritation of the gastrointestinal tract is likely, particularly if more than 0.3 to 0.4 Gm. are given in one dose. When digitalization has been accomplished, such complaints are definite symptoms of overdosage and arise in the central nervous system. If digitalis is pushed, vomiting and diarrhea occur.

Cardiac Arrhythmias: The next most important feature of digitalis toxicity is the effect upon cardiac rhythmicity. Although overdosage may produce any and all types of arrhythmia, by far the commonest and earliest warning is the onset of premature ventricular contractions. As these "extrasystoles" become more frequent, "coupling" occurs. "Coupling" is an arrhythmia in which every normal sinus beat is followed by a premature ventricular contraction. Digitalis must be discontinued immediately. If not, ventricular tachycardia, ventricular flutter, and ventricular fibrillation can and often do occur. Ventricular fibrillation almost invariably means sudden death unless heroic measures are initiated immediately.

Other arrhythmias, in order of frequency, are sinus arrest or block; sinus bradycardia; atrioventricular conduction delay to complete heart block; premature atrial beats leading to an ectopic atrial tachycardia accompanied by Wenkebach phenomena; 2:1 A-V block or erratic ventricular response and merging into auricular fibrillation or "impure flutter"; and very rarely bundle branch block. One common mistake may be easy to make. The ventricular slowing induced by digitalization in auricular fibrillation may change to a fairly fast regular rhythm. This may be interpreted by the clinician to mean conversion to normal sinus rhythm In actual practice it is much more likely to be due to an ectopic pacemaker in the A-V node or ventricles. Therefore it is a sign of toxicity. Digitalis must be withheld immediately. Any of the aforementioned arrhythmias can and will lead to ventricular fibrillation if digitalis is pushed.

Neurologic Symptoms: Neurologic symptoms are infrequent. However the clinician must be on the alert for such symptoms as the patient often does not mention them unless they are brought out by skillful questioning. The commonest symptom is a visual disturbance in which all objects appear yellow or "snowy." Spots before the eyes (scotomata) and blurring of vision is infrequent. Occasionally headaches and neuralgias of the arms and of the face appear. The facial pain may lead to unwarranted tooth extractions. Vaguer symptoms such as weakness, loss of pep, irritability, and insomnia may occur. The only proof that digitalis is the causative agent is the demonstration that withdrawal of the drug relieves the symptoms. The recent studies on placebo reactors make even this test a shaky one.

Miscellaneous: True allergic reactions must be very rare. A few cases of thrombocytopenic purpura have been reported. The frequent complaint by some patients that they can not tolerate any digitalis preparation is usually false. Secondary effects such as the appearance of gynecomastia in males is uncommon and not considered a toxic sign.

Prevention and Treatment: It is true that digitalis intoxication has become more frequent in the last two decades. There are many factors involved. The most important one is that the medical profession has come

to realize the importance of digitalis in congestive heart failure and in certain cardiac arrhythmias. This realization has led to more frequent use of digitalis preparations. Another factor has been the employment of the purified glycosides and more rapid digitalization schedules. Rapid digitalization increases the risk of toxicity.

A purified glycoside, digitoxin, has been shown to be almost completely absorbed by the gastrointestinal tract in large doses with only trivial discomfort. Serious arrhythmias and reappearance of congestive phenomena from overdosage of this drug can occur without the appearance of important toxic signs and symptoms. Digitalis whole leaf almost invariably produces premonitory intestinal symptoms, visual disturbances or "coupling" long before such serious events occur.

Another factor of major importance in the production of toxicity is the use concomitantly with digitalis of energetic diuretic regimes such as low salt diet, acidifying agents such as ammonium chloride, mercurial diuretics, resins, carbonic anhydrase inhibitors and so forth. Such "all out" therapeutic regimes lead to electrolytic disturbances that increase the hazards of digitalis medication. Examples are the production of the "low salt syndrome" with impairment of renal function, and depletion of potassium stores with enhancement of digitalis toxicity.

Finally, a motley crew of errors of omission and commission can produce serious consequences. Failure to take into consideration the possibility of prior digitalis administration; failure to look for or heed the warning signals of overdosage; failure to learn well the average rate of absorption and elimination of a few preparations, failure to take into consideration contributory factors such as hyperthyroidism, myocardial infarction, nutritional status and finally errors in diagnosis all may lead to serious over- or underdosage.

Prevention of toxicity, therefore, includes the following measures: A careful evaluation of the patient before and during digitalization, slow digitalization except in rare instances, frequent observation of the patient, a willingness to change the dosage schedule as indicated, a reasonable knowledge of the preparation employed, the avoidance of an excessive number of other measures, and a conservative attitude. If these rules are observed, digitalis toxicity is a rare event.

If minor symptoms and signs occur, the withdrawal of the drug followed by resumption of maintenance at a slightly lower dosage level is sufficient. If the symptoms and signs are more serious, the drug may need to be withheld for a longer period.

If the more serious arrhythmias occur, such as ventricular tachycardia, hospitalization and constant careful medical supervision are desirable. As the therapeutic agents and measures that may be employed are potentially dangerous, it is important to determine whether the toxicity is increasing or decreasing. The main and only danger is death from ventricular fibrillation. An electrocardiograph machine should be connected continuously to the patient in order to take frequent tracings. If it is reasonably established that hyperkalemia is not present and that renal function is adequate, potassium may be given orally or intravenously. It is difficult to produce serious toxic cardiac disturbances by the oral route while

intravenous route is potentially hazardous. Hyperkalemia causes depression of the cardiac conduction and impairment of muscular contraction leading to arrhythmias, hypotension, anoxia, and ventricular fibrillation. Other antifibrillatory agents have similar effects plus other features such as a direct peripheral vasodilation. Such agents include quinidine, procaine, procaine amide, and magnesium hydroxide.

A recommended procedure for the use of potassium is to employ a solution containing potassium chloride, 3.0 Gm. (13 m Eq./Gm.) in 20 ml. of water. This solution should be diluted to 500 ml. in five per cent glucose solution. With a normal serum potassium, 6.0 Gm. may be injected intravenously at a maximum rate of 5 ml. per minute. In frank hypokalemia, the rate and total dosage may be increased. The salt may be given orally as chloride or citrate in an initial 4.0 Gm. dose followed by 2.0 Gm. hourly for two hours.

If potassium is not available, procaine amide may be given either orally or intravenously for ventricular paroxysmal tachycardia. 1.5 Gm. may be given orally followed by 250 mg. hourly for several doses as needed. Intravenously the drug may be given continuously at the rate of 25 mg. per minute until 300 mg. has been given. The rate is then reduced to 12.5 mg. per minute.

Whether potassium or procaine amide are given, frequent blood pressure and ECG tracings are mandatory during use of the intravenous route to prevent hypotension and cardiac conduction defects. These observations may need to be made every minute. If serious hypotension develops, the infusion must be stopped. Norepinephrine should be administered if the pressure does not return promptly to preinjection levels. Elevation of the feet may be of help.

SUMMARY

In this chapter the reviewer has covered the high spots of our increasing knowledge of the invaluable cardiac glycosides. At present a wide spectrum of fast and slow acting agents are available. All possess identical actions upon the myocardium and specialized cardiac conduction system but vary in speed and duration of effect.

With the rapidly increasing span of life, more and more patients will need treatment for congestive heart failure and cardiac arrhythmias The cardiac glycosides are and will be, in the foreseeable future, the only agents that possess a specific remediable action upon the failing myocardium and certain types of cardiac arrhythmias. For that reason alone, all physicians should be able to administer the cardiac glycosides intelligently. Careful adherence to the following simple rules may be of some help in this respect.

1. Be sure that the condition is one that will respond to digitalis therapy.
2. Always ascertain how much digitalis has been given previously.
3. Always digitalize as slowly as convenient.
4. Always adjust the dose to the patient's needs.
5. Know one fast and slow acting preparation well.
6. Remember that tolerance to digitalis preparations does not occur.
7. Be on the alert for symptoms of physical and electrolyte changes that require adjustment of dosage.

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18

The Cardiac Patient as a Surgical Risk

SURGICAL CONSIDERATIONS

Physicians are frequently asked by their surgical brethren or by their patients whether the heart can stand a contemplated operation. This question is by no means as simple as it sounds and like the one put to a man on the witness stand when he was asked if he would stop beating his wife, it cannot be answered categorically "yes" or "no." It places on the physician a triple responsibility. First he must aid in the underlying diagnosis, for often a condition that is regarded as surgical may in fact be due to a disorder of the heart itself or to the peripheral circulation, for which medical treatment would be indicated. The second aspect of this problem is to ascertain if possible the prognosis of the cardiac condition that is present in order to aid in advising whether a surgical operation that ordinarily would be indicated and justifiable, should be undertaken. It is obvious that if a patient has advanced hypertensive heart failure he should not be subjected to an operation such as repair of an abdominal hernia. This requires the intelligent appraisal of the cardiac state and an attempt to foretell how long a patient may be expected to enjoy the benefits of the surgery that is planned. Finally, when an operation is decided upon in one suffering from some form of heart disease, the physician may aid in estimating with what added risk a particular cardiac abnormality is attended and in what way the risk might be minimized. The above questions therefore entail a close cooperation between the surgeon and physician permitting a free and detailed analysis of all the factors concerned.

Differential Diagnosis: Let us first consider some of the difficulties that arise in differential diagnosis, in distinguishing what appears to be an acute surgical abdominal condition from disorders that are produced directly by the heart or cardiovascular system. In former years it was not an infrequent experience to confuse acute coronary thrombosis and myocardial infarction with acute abdominal emergencies such as perforated peptic ulcer, acute pancreatitis, acute disease of the gallbladder, diaphragmatic hernia, acute intestinal obstruction, etc. There is hardly any active surgical clinic that has not made the error of exploring the abdomen when the cause of the epigastric pain, vomiting and collapse was a thrombosis of the coronary artery. This confusion was discussed many years ago[1] since which time much has been learned to help us avoid similar

blunders. In fact our knowledge concerning diagnosis of coronary artery disease has become so extensive that at present there is possibly greater danger of overlooking abdominal conditions that require immediate operation when this type of differential diagnosis arises.

There are certain precautions that may help in this decision. Realizing that severe epigastric distress or pain may be due to disease of the heart or of the abdominal organs, a previous history of angina, which often has to be deliberately inquired for, lends some support to the former as the cause in any particular case. Pain from coronary artery disease even when localized in the abdomen tends to radiate up the sternum or to the arms and almost never extends below the umbilicus. It is also often associated with dyspnea. *One should always suspect the abdomen when this differential problem arises in a woman if it is known that the patient was not hypertensive.* This general rule does not apply in the male sex.

Finally the electrocardiogram which now can be taken so readily at the bedside, may give invaluable information. Although there may be pathognomonic changes pointing to myocardial infarction, great caution needs to be exercised in reading too much into less distinctive alterations in the form of the ventricular complex. There will be instances that tax all our diagnostic resources including x-ray plates of the abdomen looking for free gas below the diaphragm. It is needless to go into a complete discussion of all the conditions that may arise, for they are numerous. Suffice it to recall that many of the common acute abdominal conditions may be confused with an attack of atypical coronary thrombosis.

Similarly there are occasional instances when the acute development of congestive heart failure can present the picture of an acute surgical condition of the abdomen. This is apt to occur with the sudden onset of auricular fibrillation, especially in a previously undigitalized heart. If mitral stenosis is present, and it may not have been recognized or easily detectable, acute pain and spasm in the epigastrium or right upper quadrant, slight fever and leukocytosis, nausea, vomiting, and even slight jaundice may result. The presenting findings in such cases probably are the result of acute congestion of the liver with stretching of its capsule and may be misjudged as due to acute cholecystitis. The therapeutic decision is not very difficult as ordinarily there is no great haste about surgery for disease of the gallbladder, and the presence of a rapid irregular heart rate in any case deserves digitalis therapy and other treatment for heart failure, if evidence of congestion is found. When the above symptoms are due to the heart they will promptly be relieved by appropriate cardiac therapy.

In younger patients acute pain in the abdomen, resembling that due to acute appendicitis, may occur in rheumatic fever. The pain need not be very severe but can be accompanied by nausea, some localized tenderness and vomiting, slight fever and leukocytosis and in many ways imitate very closely what is found in acute appendicitis. At times it will be impossible to distinguish the two conditions with any certainty and an exploratory operation will be unavoidable and should be regarded as the correct procedure even if it turns out to have been unnecessary.

Some of these operations will be unavoidable for *there is greater risk in delay when the appendix is inflamed than in an abdominal exploration when mild rheumatic fever is present.* There are times, however, when careful attention to details will reward the physician by enabling him to make a more definite diagnosis. Rectal tenderness is much more apt to indicate appendicitis, as it is quite rare in rheumatic fever.

Of greater importance in these cases of atypical rheumatic fever with abdominal symptoms but without pains in the limbs, are the direct findings in the heart. One may detect distinct abnormalities in the heart that occur with particular frequency in rheumatism and are rare in other conditions. The finding of a loud systolic murmur or a diastolic murmur that was not previously present, a pericardial friction rub, or the detection of delayed A-V conduction time (increased P-R interval in the electrocardiogram) would make the diagnosis of rheumatic fever fairly certain. I recall an instance in which the surgeon heard a peculiar sound over the precordium which he was unable to interpret. This proved to be a gallop rhythm which in children should always make the physician suspect a delayed P-R interval (or first degree heart block). This turned out to be the case and the young girl recovered on salicylates, thereby avoiding what might have been an ill-advised operation.

Other medical conditions that may present themselves with what appears to be an acute surgical abdomen are pneumonia and acute pericarditis. These acute inflammatory processes in the thorax, especially when they occur in childhood, may first manifest themselves with abdominal pain and vomiting. Only the scrupulous care of a thorough physical examination and the constant recollections of these possibilities in differential diagnosis will prevent the confusion that otherwise will take place. Similarly the rare cases of tabetic crises, lead colic and other nonsurgical conditions must be sought for when the cause of abdominal symptoms is being investigated.

Significance of Symptoms: In appraising the significance of abdominal or other symptoms that appear to have surgical implications, the possibility of embolism must not be forgotten. One should have this particularly in mind under the following four conditions: Auricular fibrillation, mitral stenosis, coronary thrombosis with myocardial infarction and bacterial endocarditis. With the first two, sterile thrombi form in the auricles; with the third, in the ventricles and with the last, infected vegetations are present on the valves. If parts of these thrombi become dislodged, embolism develops When such emboli involve the renal, splenic or mesenteric arteries, abdominal symptoms result. Careful examination of the cardiac state will prevent the physician, at least, from overlooking these nonsurgical causes of abdominal symptoms.

Prognosis versus Surgical Risk: The second aspect of this problem is whether the prognosis of the cardiovascular state is good enough to warrant the contemplated surgical operation. Is the patient with a particular type of heart disease going to live long enough to enjoy the results of the surgery? This is entirely a matter of prognosis and here judgment is difficult. Those operations which in themselves help the embarrassed

circulation are always better borne and will be more beneficial in their end results than when there is no direct relation between the surgical and cardiac conditions. A patient with mitral stenosis, auricular fibrillation and hyperthyroidism in advanced congestive failure for example, will actually show marked improvement in the heart following a subtotal thyroidectomy. It would be unwise in such a case, on the other hand, to advise an operation for repair of a cystocele. In patients with angina pectoris, occasionally, the cardiac state seems to be improved following the removal of gallstones or after the relief of prostatic obstruction. Apart from the cases in which the heart itself may be more or less improved by the operation, great care must be exercised in not advising major surgical procedures for those conditions which are not urgent or for which there are available adequate nonsurgical or palliative measures. When one would judge the life expectancy of a given cardiac disease as one to two years, it is illogical to advise a hysterectomy for fibroid tumors of the uterus when x-ray treatment may control the menorrhagia. If a patient has had hypertensive heart failure and shows a bundle branch block or gallop rhythm or pulsus alternans it is better to temporize with a truss than to operate for an ordinary inguinal hernia. Removal of teeth and tonsils and procedures such as pelvic operations for prolapse of the uterus or a relaxed pelvic floor may be avoided when contemplated in those suffering from grave heart disease. An illustration of such a problem is the following experience:

A woman, aged forty, complained of lower abdominal discomfort and excessive uterine bleeding. She had luetic aortitis and aortic insufficiency. She also showed evidence of a large uterine fibroid which could barely be felt above the pubis. A hysterectomy had been advised by another physician. Because of her cardiac condition it seemed wiser to try x-ray treatment. This was carried out and caused cessation of her menstrual periods and the tumor could no longer be felt A simple method without risk achieved the same therapeutic result as the contemplated surgery.

In all these matters the intelligence of the physician must be used, weighing all the circumstances pertaining to the prognosis of the type of heart disease that is present and the amount of discomfort and hazard from the surgical conditions.

Estimation of Surgical Risk: The final phase of this problem is the estimation of the risk that a patient with heart disease undergoes in a major surgical operation. *There has been altogether too much fear concerning the ability of the heart to withstand operations.* When postoperative deaths have occurred physicians have been too prone to ascribe the cause to the heart. In all fatal cases, death occurs when the heart stops, but that is by no means synonymous with death from heart failure or heart disease. On close scrutiny it will be found that in only a few instances can the heart be blamed as playing even a contributing role in the cause of the fatality.

Let us first consider what changes take place in the heart during an operation. Marvin and Pastor[2] found that there was no constant change in the blood pressure during or following operations. In some the pres-

sure rose and in others it fell. They decided that the only instances in which the change in pressure materially affected the incidence of untoward complications were those in which there was extreme lowering of the blood pressure and pulse pressure with a state of shock. It was also found[3] that routine preoperative administration of digitalis failed to exert a favorable influence on the blood pressure or on the incidence of postoperative complications. In fact there was suggestive evidence that digitalis may have a slightly deleterious effect. On the other hand Blalock[4] found that the average output of the dog's heart during ether administration was increased seventy-six per cent. In this experimental investigation it was also found[5,6] that the increase in the cardiac output could be diminished by the use of alkali or digitalis. From these experiments it would seem that the work of the heart might be temporarily increased during surgical operations. However, in actual surgical cases Snyder[7] found an average decrease of forty-one per cent in cardiac output directly after operations while the patients were still under the anesthetic, and that it required one to four days for the output to return to normal. How material these various effects might be in the operative risk can only be ascertained by clinical experience.

Brow and Long have shown[8] that chloroform, ether, nitrous oxide and barbiturate derivatives when used to produce anesthesia in cats, cause a decrease in glycogen storage and an accumulation of acid metabolites (lactic and phosphoric acid) in cardiac muscle. Furthermore, disturbances in the mechanism of the heartbeat have been observed during anesthesia. Levy[9,10] noted in cats the development of extra ventricular systoles, ventricular tachycardia and ventricular fibrillation at certain low concentrations of chloroform anesthesia. He thereby explained the mechanism of sudden death which occurred under chloroform. In routine operations on *surgical patients during anesthesia produced by ether, nitrous oxide or* procaine, Lennox, Graves, and Levine[11] observed frequent abnormalities of the heartbeat such as premature beats, dislocation of the pacemaker especially resulting in nodal rhythm and even paroxysmal auricular tachycardia. These were found to be transient and with very rare exception were of physiological rather than clinical interest. Only on rare occasions did the development of a new rhythm during an operation produce alarming symptoms. A study of such disturbances[12] has shown that they are due to paroxysms of auricular tachycardia, auricular fibrillation or auricular flutter. When properly recognized, they are easily controlled by carotid sinus or ocular pressure or by the use of such drugs as mecholyl, digitalis, or quinidine Despite the above physiological and chemical alterations which take place during anesthesia and operations, how much harm they produce can only be determined by studying the incidence of postoperative complications and fatalities in cardiacs and noncardiacs. This is the only method available to determine the surgical risk of various types of heart disease.

Extensive experience during the past two decades has afforded adequate proof that patients with heart disease, on the whole, withstand surgical operations very well. The old fears concerning the heart, although

they still persist in the minds of the laity and to a slight extent of the medical profession, have largely disappeared. A review of over 400 patients[13] suffering from organic heart disease, who were subjected to various major surgical operations, showed that the unexpected mortality was only 6.4 per cent. Furthermore, on investigating the cause of postoperative death in cardiacs it becomes evident that death results, for the most part, from the same complications that occur in noncardiacs,[17] *i. e.*, postoperative pulmonary complications, shock, infection, etc. True cardiac failure is rare although some of the so-called accidents of heart disease such as coronary thrombosis and pulmonary and peripheral embolism do occur more frequently.

In estimating the risk which a given cardiac condition adds to that of the contemplated operation there are two important factors to be considered. The first and by far the most important is the ability of the heart to respond to effort. If the cardiac condition has been well compensated, if the patient has been able to carry on his ordinary duties, the heart has already given evidence of withstanding a greater load than any operation will demand. This has reference to the heart and not to the peripheral circulation, for the latter may fail with equal facility whether the heart is diseased or not.

If follows, therefore, that the history pertaining to cardiac efficiency is much more important than the physical examination of the heart. The presence or absence of breathlessness is much more informing than whether a murmur or some cardiac hypertrophy is present. The second important factor is the liability of that particular heart to the so-called "accidents" of heart disease. These are the unpredictable complications that occur which suddenly change the entire status and prognosis of the situation. Amongst the latter are the development of acute coronary thrombosis, embolism, sudden changes in cardiac rhythm such as Adams-Stokes attacks or paroxysmal rapid heart action, bacterial endocarditis and sudden death possibly due to ventricular fibrillation. Fortunately such postoperative complications are not very common though they do occur. One can classify cases into those that are more and those that are less likely to develop these complications, but it is impossible to foretell events in individual instances.

Because it is mainly the above "accidents" of heart disease that increase the operative risk of cardiac patients, it is of some interest to analyze the circumstances under which they may arise. Coronary thrombosis can occur in anyone suffering from coronary artery sclerosis. The main clinical evidence of this will be the history of angina pectoris. Therefore, it becomes extremely important to inquire most carefully into those symptoms that characterize the anginal state. Often when a postoperative coronary attack has occurred, apparently in one who was regarded as previously having a normal heart, it later becomes evident on close scrutiny that there was a definite history of sternal constriction on effort which had been entirely overlooked. Even some sudden and instant postoperative fatalities will prove to have a similar explanation.

Embolism from the heart mainly comes from sterile mural thrombi,

from the auricles in cases of auricular fibrillation or of mitral stenosis and much more rarely from the ventricles in cases of myocardial infarction. The presence of these conditions, therefore, predispose to such complications. Complete heart block obviously is the most common condition in which sudden Adams-Stokes attacks may occur, but the various types of paroxysmal rapid heart action may develop in patients with otherwise normal hearts although more frequently in those with *organic heart disease. Postoperative bacterial endocarditis is very rare* but may develop in one who previously gave evidence of a well-compensated, regular heart and in whom there was some kind of cardiac murmur. Such disastrous complications have been observed particularly after tonsillectomy or extraction of teeth possibly because these simple operations are so common. They are now either preventable by prophylactic use of antibiotics or responsive to chemotherapy, should they arise

Notwithstanding the various hazards to which patients with heart disease are subject, on the whole, the operative risk is rather small. An operative mortality of 2.1 per cent in 147 cases of valvular disease and of 3.0 per cent in 103 cases of auricular fibrillation[13] indicates how satisfactorily cardiacs tolerate major surgical procedures. The risk increases, however, under certain circumstances. Cases of angina pectoris, for the most part occurring in the second half of life, carry a risk of 7.7 per cent. This is mainly due to the postoperative development of coronary thrombosis, a subject emphasized by Master and associates[15] The danger is still greater amongst those who have already suffered a previous attack of coronary thrombosis. The proper timing of operations and selection of *cases should even here keep the rate about ten to fifteen per cent.* The presence of congestive heart failure adds decidedly to the risk of operation but except for emergencies, adequate preoperative medical treatment will decidedly reduce this risk. Although hypertension has little effect on the mortality rate the presence of chronic nephritis increases it threefold In general it may be said that *all cardiacs do surprisingly well except for those who have nephritis, congestive failure or coronary artery disease.*

So far no mention has been made about the type of anesthesia in its relation to the operative risk in cardiac patients. There has been no extensive analysis of the relative merits of different anesthetics for those suffering from organic heart disease. Our opinions, therefore, rest upon general impressions rather than convincing data. Differences in point of view amongst different observers probably signify that the matter is not of great importance Marvin[16] very wisely stated "that it is far more important to select the proper anesthetist than it is to select the proper anesthetic." The choice will generally be determined after a consultation between surgeon, anesthetist and physician with the goal that a smooth, shockless anesthesia may be obtained. Ether, avertin, ethylene, spinal, and local anesthesia each have their advocates. The important factors that seem to be material are to avoid struggling, the collection of mucus in the upper respiratory tract and cyanosis and to prevent a maintained fall in blood pressure. The disadvantages of the former are obvious and

there is reason to believe that a significant fall in blood pressure, apart from being a forerunner of surgical shock, is conducive to the development of coronary thrombosis. It is for this latter reason that, when spinal anesthesia is used in elderly patients who often have coronary artery sclerosis, great care should be taken to prevent any untoward fall in the pressure level. In general, I prefer ether anesthesia in cardiac patients, although there are reasonable differences in views amongst reputable authorities.

In conclusion, it may be stated that intelligent cooperation between physician, surgeon and anesthetist will enable most patients suffering from heart disease to undergo surgical operations with only slightly greater risks than prevails in noncardiacs. It will also avoid ill-advised operations on cases that present features resembling surgical conditions which in point of fact are due to some form of cardiovascular or nonsurgical disease. Proper preoperative care and timing of the operation, when possible, will diminish the surgical risk. Finally, careful diagnosis and prognosis will eliminate many unwise operations for which palliative nonoperative measures are available when the patient might not be expected to live long enough to enjoy the results of the surgery.

OBSTETRICAL CONSIDERATIONS

The problem of the cardiac patient and pregnancy has many ramifications. The physician has to consider not only the purely medical aspects of the case but also religious, social and economic factors. Decisions will therefore have to differ even when the physical condition of the heart may be the same, depending on these other factors. The whole problem is one in which the medical profession has made considerable progress. The application of modern methods of diagnosis and treatment of heart disease and the institution of a systematic control of cardiacs who may become pregnant has decreased the maternal mortality amongst organic cardiacs during the past several decades from about twenty per cent to about three per cent.[17] By the proper selection of patients who should become pregnant and the intelligent care during pregnancy, many lives are now being saved that were previously sacrificed.

Effect of Pregnancy on Normal Heart: Let us first consider the effect of pregnancy on the normal heart. Studies of the dynamics of the circulation[18,19,20] have shown that there is a decided gradual increase in the work of the heart during pregnancy. This reaches its maximum of fifty per cent increase at the eighth month. The blood volume and the minute output of blood increases and the velocity of blood flow accelerates. The blood pressure normally does not increase (in fact it often is quite low) but during the pains of labor it may rise producing a further temporary increase in the work of the heart. During the ninth month adjustments in the circulatory dynamics occur which somewhat lighten the cardiac burden from the high point reached the previous month.

Care of Heart Disease in Pregnancy: Of primary importance in the care of pregnant cardiacs is accurate diagnosis of the condition of the heart. When heart disease is present in association with pregnancy the

overwhelming majority (ninety per cent) will be found to have rheumatic valvular disease, a few will have hypertensive, luetic or congenital heart and very rarely one may have coronary artery disease. The main discussion, therefore, will concern rheumatic heart disease. There are many pregnant women who present features resembling those seen in organic heart disease that are functional in origin and may be called neurocirculatory asthenia or cardiac neurosis. They may have faint systolic murmurs, rapid heart rates, dyspnea and palpitation. In addition there may even be some puffiness of the ankles from the pressure of the gravid uterus without any structural disease of the heart. Such patients can quickly be separated and treated as normal pregnant women. Great care, therefore, must be exercised before classifying the case as one with organic heart disease.

The second group to distinguish consists of those who have simple mitral insufficiency. In this group a moderately loud or loud systolic murmur will be audible at the apex not explicable on any other basis. There generally will be a past history of rheumatic fever or chorea and possibly slight cardiac hypertrophy. If there is no diastolic murmur whatever *and no other signs of mitral stenosis it may properly be classified as* one of mitral regurgitation. When such cases are well compensated and show no objective or subjective evidence of congestive failure, for obstetrical purposes they may be regarded as normal women, for the maternal mortality will be about one per cent.

The third group consists of those showing definite evidence of mitral stenosis or of aortic valvular disease. Amongst the former will be some with auricular fibrillation. The signs of mitral stenosis may be obscure and require most careful auscultation. Some will show signs of both aortic and mitral involvement. This is the most important group of all, for here the problem of congestive heart failure arises and there will be a significant maternal mortality

In order to outline the practical methods in the care of pregnant cardiacs let us trace the steps of a married woman who contemplates pregnancy. At the outset she should visit a physician for a complete physical examination. If she does not fall into the third group, *i. e.*, she has no organic heart disease or only has mitral insufficiency she may become pregnant without any undue apprehension and can be treated as a normal patient If she belongs to group three, *i. e.*, shows signs of mitral stenosis, aortic valvular disease, or one of the less common types of organic heart disease, an estimation of the state of compensation should be made. The early evidence of decompensation will mainly be dyspnea on exertion not previously experienced, cough on effort, rales at the bases of the lungs, hemoptysis or the presence of auricular fibrillation. A decided reduction of the vital capacity of the lungs, especially when its previous level is known, is a very reliable index of congestive failure. It is striking *that in normal or well-compensated cardiacs the vital capacity* of the lungs is not diminished even when the abdomen is enlarged by the full-term fetus When it is found that decompensation is absent, the patient may be advised to become pregnant or be permitted to carry on

if already pregnant. Contrariwise, if there has been a history of decompensation in the past, or there is present evidence of cardiac failure or if persistent auricular fibrillation is found (omitting the rare instance of this arrhythmia in an otherwise normal heart) pregnancy should be avoided or interrupted. The advantage of early and frequent examination is that abortion during the first few months is a comparatively simple procedure whereas during the last few months it is a major one.

As the pregnancy continues, the patient should be cautioned against overexertion or becoming unduly fatigued. Tiresome shopping should be prohibited. Respiratory infections should be avoided as far as possible and any apparently minor infection requires more than the customary care in bed. If any evidence of heart failure develops in the later months of pregnancy, the patient will need to be more or less in bed the remainder of the pregnancy. Even when treatment results in restoration of compensation, activities should be restricted to a bed and chair existence with very little more until after the delivery.

The advice given to cardiacs will differ materially depending upon the number of children there are already. In the absence of decompensation or other evidence of grave heart disease all cardiacs should be allowed to go through their first pregnancy. In fact, they should be urged to have their baby soon. The heart does not get better with increasing years and the mother will live longer to enjoy the life with the child than if pregnancy is delayed. Furthermore, when a normal viable child has been obtained without any difficulties, it is wise to advise such a patient to have a second child within the next two years. Most parents want more than one child and it is better to make the final decision about this matter immediately than to have it come up five years later. The question of a third child, providing that compensation has remained satisfactory, is entirely optional with the parents. When there are already three normal children there is good reason to advise cardiac mothers to avoid any further pregnancies. Although there are numerous instances of women with mitral stenosis surviving six, eight or ten pregnancies, there are a good many others who have succumbed. Under the best circumstances the risk is greater than normal for any cardiac who belongs to group three. There is, therefore, a definite indication for the use of contraceptives in all cases of organic heart disease when there are already three children or for performing abortion if pregnancy has already occurred. *There is very little evidence to show that cardiacs going through pregnancies without failure of the circulation shorten their lives.* Reid[21] showed that married women suffering from heart disease who had borne on the average more than five children died at an average age only slightly less than unmarried cardiacs. In all these considerations due attention must be paid to the wishes of the parents, their religious restrictions and the economic and social status of the household, bearing in mind that the actual bringing up of several children is a considerable task on a diseased heart.

Sterilization should never be performed unless it is absolutely certain that no more pregnancies are to be permitted. It is generally unwise to perform sterilization at the time of the first pregnancy, for the child may

not survive the first few days or may be an abnormal child. On several occasions I have seen well-compensated cardiacs, who had a cesarean section at the time of their first pregnancy and had their tubes tied, who lost their babies during the first twenty-four hours. They were in a sufficiently good state of compensation readily to have gone through subsequent pregnancies, but had to remain childless the rest of their lives. Furthermore, a cesarean operation should not be advised merely to enable the obstetrician to sterilize the patient. This should be done at a later time if advisable. Notwithstanding the fact that there is some difference of opinion amongst obstetricians, I favor the opinion that the procedure of choice is delivery by the pelvic route unless there are obstetrical indications for an abdominal section. The second stage of labor should be abbreviated by the use of low forceps. The type of anesthesia is not of great importance although cardiacs in general do well with ether. If an abdominal operation is decided upon and there is or has been cardiac failure or a sufficient number of children have already been born, sterilization should be performed at the same time.

It is obvious that women who are in congestive failure should not become pregnant and should be aborted during the first two or three months of pregnancy. But if they are first seen in gross failure after the fifth month or develop failure in the latter months of pregnancy, most painstaking cardiac treatment should be carried out to reestablish adequate compensation or at least to carry the mother far enough to obtain a viable child. To avoid the development of congestive phenomena in those suffering from major cardiac disease the salt intake should be restricted but protein should be given liberally and iron as well if necessary. Hypoproteinemia and anemia are potential factors that may further embarrass the circulation and often can be readily prevented.

The value of carefully classifying cases according to diagnosis and functional capacity is well brought out by the statistics compiled by Pardee.[22] He reported no deaths amongst 157 organic cardiacs who showed no evidence of failure on considerable effort, 1 death in 180 patients with only slightly restricted activities, 8 out of 169 who were greatly limited in their response to effort and 16 out of 40 who were essentially bedridden. The results published by Fitzgerald[23] and Hamilton and his collaborators[17,24] are all in accord with these results. Despite these excellent results unexpected and unpredictable disasters can occur. At times congestive failure develops even in the form of acute pulmonary edema when everything pointed to a favorable course. The latter may require morphia and even phlebotomy and oxygen therapy. Digitalis would also be indicated. Rarely subacute bacterial endocarditis used to be a fatal complication but now is amenable to penicillin therapy. These complications, apart from those to which normal pregnant women are subject, are responsible for the small but irreducible mortality of pregnancy in cardiacs.

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BURTON E. HAMILTON, M.D.

19

The Cardiovascular Patient in Pregnancy

SIGNIFICANCE OF PREGNANCY TO WOMEN WITH CHRONIC HEART DISEASE

From the Medical Point of View: Many young women with chronic heart disease even nowadays do not know they are cardiacs till married and pregnant. Since most young women cardiacs marry and then nearly all undertake pregnancy, school and premarital examinations should be thorough enough to reveal the cardiacs. They should be given timely information so that they can intelligently decide whether they will marry, and with their husbands, decide whether to undertake pregnancy. This holds for therapeutic abortion, within the law and medical ethics. It is *the physician's function to inform the principles, not to make the decision* for them, nor to advise Pregnancy is not a disease. It is more or less desirable to each individual patient.

From the Obstetrical Point of View: In regions where rheumatic fever is prevalent, close to one in seventy pregnant women have chronic heart disease. This small percentage of all pregnant women has furnished a much higher percentage of all the obstetrical deaths.

The Risks of Pregnancy for Cardiacs: When a heart clinic was started at the Boston Lying-in Hospital, the maternal death rate for cardiacs had been between fifteen and twenty per cent. Two to three years after the heart clinic was started, a system for detecting heart disease early in pregnancy and for special care for the patient had developed. The death rate then fell critically to approximately three per cent. Similar critical drops in maternal death rates for cardiacs have been reported by other obstetrical clinics after they started similar cardiac clinics This puts the responsibility for the cardiac in pregnancy and puerperium squarely on the shoulders of the physician or cardiologist working with the obstetrician.

Statistics from the Boston Lying-in Hospital Cardiac Clinic have been carefully reported at times since 1921. In summary, they are·

Approximately ninety per cent of all the pregnant women who are cardiacs have chronic rheumatic heart disease; three per cent have congenital cardiovascular defects, the remainder includes all the other cardiac diseases, such as cardiovascular syphilis, thyroid heart, deficiency heart, premature atherosclerotic heart disease, and serious disorders of the heart beat. Patients with hypertension and no other cardiovascular disease are

not included. The following applies particularly to the great majority of the cardiacs—those with chronic rheumatic heart disease.

The maternal death rate for all those with chronic rheumatic heart disease delivered at the Boston Lying-in Hospital for twenty-five years after the cardiac clinic started was between three and four per cent. Since the risk of individual cardiacs varies greatly, useful advice to an individual calls for as accurate subclassification as can be made. In simplest form, the problem of estimating a cardiac patient's risk from pregnancy is whether the heart can fulfill the normal demands of pregnancy if she has all possible needed treatment designed to lessen the work of the heart. If a patient has led a reasonably normal life, has been able to carry on in school and to work in a factory or shop, or as a secretary or teacher, or to go about socially to dances, and so forth, without congestive heart failure—even if she has avoided heavy demands on the heart such as climbing, running, swimming, tennis, because breathlessness prevented her from keeping up with her companions,—the chances are that with a careful regimen, enough work can be taken off her heart to compensate for at least the usual demands of normal pregnancy. But if she has had congestive heart failure under ordinary circumstances, the chances are that she will have difficulty in avoiding a return of failure even under the best treatment. Although it is difficult to define congestive heart failure and sometimes difficult to know from the history whether a given patient has had congestive heart failure, it is usually easy to decide this point.

If a patient with heart disease has some other defect such as chronic nephritis, pyelitis, tuberculosis, etc., she would be a poor risk for pregnancy. Two diseases are worse than the sum of the risks of both diseases For illustration, the maternal death rate in pregnancy for uncomplicated mitral stenosis is approximately 2.5 per cent; for uncomplicated eclampsia in previously normal women, approximately ten per cent. The maternal death rate for mitral stenosis complicated by eclampsia, however, is not 12.5 per cent but approximately forty per cent. The significance of this point in treatment of cardiacs will be discussed later.

It has long been known that cardiacs who have auricular fibrillation are comparatively poor risks for pregnancy.

One can, then, distinguish a group of cardiacs who have led reasonably normal lives and not had congestive heart failure, who have no significant complicating disease, who do not have auricular fibrillation, and consider the group "favorable" for pregnancy. More than eighty-five per cent of the cardiacs at the Boston Lying-in Hospital are, by these criteria, "favorable." There is a small group left that have had congestive heart failure, or have a complicating disease, or have auricular fibrillation, who are "unfavorable" prospects for successful pregnancy.

On this basis, the maternal death rate for "favorable" cases for the year of a pregnancy and puerperium, in my experience, is between 2 and 2.5 per cent. The yearly death rate for similar cases when not pregnant is slightly less. The maternal death rate for "unfavorable" cases has been approximately sixteen or eighteen per cent, whereas their yearly death rate when not pregnant has been from six to seven per cent. For patients

with chronic heart disease who have auricular fibrillation, the maternal death rate has been close to 33 1/3 per cent, but only eight per cent yearly when not pregnant. Infant mortality jumps from, roughly, eight per cent in the favorable group to thirty per cent in the whole unfavorable group and fifty per cent for those that have auricular fibrillation.

Occasionally, one encounters statistical reports indicating that the risk for cardiacs in pregnancy is much lower than this, and, from some reports, incredibly low. It is difficult to collect accurate statistics on this matter. In general hospitals, cardiacs before delivery are treated in medical wards, and if they die undelivered, they do not appear in the obstetric service's deaths. If delivered and doing well, they are discharged from the obstetric service as successful cases and if their cardiac condition is poor after delivery, they are sent to a medical service, as they should be. Only those who die quickly and after delivery, die on the obstetric service. If one is in doubt about the accuracy of the statistics given here, it is reassuring to know that almost identical statistics have been obtained simultaneously in similar heart clinics in other obstetric hospitals—for example, the Sloane Hospital for Women in New York City.

All cardiacs differ from each other in many ways, especially in their capacity for effort. Patients are more or less "favorable" or "unfavorable" for pregnancy. But the statistics given above show the value of this simple classification. We can only estimate the risk of an individual in each group as she seems better or worse than the average favorable or unfavorable case. In my experience, patients over thiry-five years of age are twice likely to have congestive heart failure as are those younger; whereas patients under twenty-three years of age are many times more likely to have a recurrence of rheumatic fever than the older patients. The patients with uncomplicated aortic regurgitation have little if any greater risk than those with mitral stenosis. Those with aortic regurgitation are, however, more troublesome than those with mitral stenosis because of the tendency of the former to have good capacity for effort until the onset of severe left ventricular failure. They have little warning of disaster. Patients with both mitral and aortic involvement are only slightly worse risks than those with either valve alone involved. But patients with a systolic murmur, no diastolic murmur, and definite enlargement of the heart are twice as good risks, as those with aortic regurgitation, mitral stenosis, or both. Gross enlargement of the heart is certainly not a favorable finding, but I have not been able to express with definite statistics the estimation of risk on heart size. We may feel sure of the value in subclassification of the three groups as defined above, "favorable," "unfavorable," and the small group of cardiacs that have auricular fibrillation, and need not feel great concern for further subclassification because care of the patient dominates all the other factors in maternal mortality in the large group that are defined "favorable" cases for pregnancy With suitable individual care, we can make their mortality rate low. The great drop in maternal mortality of the whole group came after we had learned the details of their care and applied the knowledge effectively, and the drop was from a lessening of the number of deaths from congestive heart

failure in the favorable group. The chance now for a favorable cardiac under suitable prenatal management to die from congestive heart failure in pregnancy and puerperium is little more than 1 in 500; whereas two-thirds of the deaths of the "unfavorable" cases are directly due to this. Try as we may, we cannot make the "unfavorable" cases good risks.

The maternal mortality for unfavorable cases for the first fifteen years at the Cardiac Clinic at the Boston Lying-in Hospital was sixteen per cent; it was eighteen per cent for the succeeding ten years, despite, as we hoped, improved technic in their care. The maternal mortality for cardiacs with auricular fibrillation was also no better for the ten or twelve years following the first sixteen years. It was approximately one death for every three patients.

In my experience the causes of death in the cardiacs can be listed as congestive heart failure, embolism, or subacute bacterial endocarditis The last is now a rarity. In approximately twenty-five per cent of the deaths obstetrical or coincidental complications, not related to the pregnancy directly, have been a material factor.

Control of Congestive Heart Failure in Pregnancy: An individual daily regimen is essential. In general, it should call for nine or ten hours in bed each night, and a rest in the morning and in the afternoon. The number of flights of stairs should be limited, and only the lightest housework allowed. It is a good plan to allow no shopping or activities outside the house except when the patient is transported, although exceptions may be made for thoroughly favorable patients during the first two trimesters. During the latter months of pregnancy when the load on the circulation is heaviest, it is often wise to keep a cardiac at home, and on one floor, and to allow no housework whatever. Cardiacs in pregnancy do not need exercise No harm comes from overtreating them. The burdensome part of pregnancy lasts only a few months, and one can overtreat the cardiac during this short period with a clear conscience, for the greater safety of mother and child.

Weight Control and Nutrition: A good plan is to keep weight gain throughout pregnancy to less than 6.8 kg. (15 pounds). Some have had no apparent harm and probably great benefit with much less gain than this. The intake of foods that we believe nonessential such as rich desserts and sweets should be reduced. Thin milk, lean meats, poultry, fish, vegetables, and fruits except those that are "twenty per cent" or higher, should be allowed and supplemented by vitamins, iron, and calcium. We should bear in mind the rule that two burdens are greater than their sum. Disproportionate improvement will then follow removal or partial removal of one of the burdens. For example, 4 kg. (10 pounds) of excess fat or moderate fatigue from insufficient rest are nothing much to a healthy normal human under usual conditions. Either may mean the difference between success and failure to the hard-pressed athlete at the end of a race or fight, or to anyone in a severe illness, and under all conditions to the severely handicapped cardiac. Therefore, remove or lessen any extracardiac burden that one feasibly can, and do it with enthusiasm.

These general rules are fundamental to the prevention of congestive

heart failure in cardiacs in pregnancy. It was largely due to the application of these principles that the maternal death rate for cardiacs fell abruptly and critically many years ago when cardiac clinics were started at the Boston Lying-in Hospital and at other similar institutions. There are much more novel and interesting aspects of the problem of cardiacs in pregnancy, but none is more important for their welfare.

Special Load of Normal Pregnancy on the Heart: Careful studies have shown that in pregnancy the circulating blood volume increases and the circulation becomes hurried—cardiac output increases. Pulse rate quickens, the blood pressure tends on the average to fall a little and the pulse pressure widens. Oxygen consumption, respiratory rate, tidal air increase. Vital capacity and basal metabolism do not increase proportionately so much as circulating blood volume. Circulating blood volume changes appear to be a good gauge of the load of normal pregnancy on the circulation Roughly, the circulating blood volume at its peak during pregnancy is almost fifty per cent higher than early in pregnancy. These physiological phenomena, normal in pregnancy, appear only to a small degree in the early months except in unusual cases, and in the last few weeks of pregnancy they normally recede (except the oxygen consumption). Roughly, half the increase in circulating blood volume recedes during the last four weeks. Congestive heart failure, when it occurs for the first time in pregnancy, rarely appears before the sixth month, or during the ninth calendar month, or at or after delivery. A curve representing the times in pregnancy when heart failure has first appeared resembles closely a curve showing the average variations in the extent of the average load of normal pregnancy on the circulation as determined by direct studies of the phenomena mentioned above, particularly the circulating blood volume.

Significance of the Curve of the Load of Pregnancy on the Heart: Formerly, it was believed that the load on the circulation of normal pregnancy rose gradually toward a peak at term When it was proven that on the average the load does not grow heavy before the sixth month and then rises abruptly and stays close to its peak until the last four weeks when it normally lessens to, roughly, half its rise, a number of general rules for the care of the cardiacs became clear.

It has been a rule at the B.L I Hospital that cardiacs must be seen often in pregnancy—at least once a week. It is not safe to select good risks, give them general rules, and let them go their way with only the usual number of prenatal examinations, unless symptoms force them to call for help. Though the average curve of the load of pregnancy rises at the sixth month and begins to fall at the end of the eighth, a few patients appear to feel the effect of the load very early in pregnancy, others later, and in some the rise of the load is abrupt, in others gradual, and in none can the course for an individual be correctly predicted However experienced a physician may be, he must examine each patient often through pregnancy if he is to know how she is tolerating the strain. Furthermore, case histories of patients dying of heart failure in pregnancy often reveal that the symptoms of failure appeared and became severe days or weeks before the physician knew of it.

It is natural when one sees a woman early in pregnancy to speculate on whether she can stand delivery. Actually, delivery is not her greatest test. Few heart failures occur for the first time at or after delivery unless there is a complication inflicting excess work on the heart such as fever, anemia, toxemia, or unless labor is unusually long and difficult.

Nevertheless, patients who are in congestive heart failure do not tolerate delivery well. It has long been known that cardiacs in congestive failure are not immediately relieved of their symptoms by emptying the uterus. In fact, they are more dyspneic and show more evidence of venous congestion. If they recover, they do so slowly over days or weeks, and in some reported series including one from the Boston Lying-in Hospital, more fatalities have occurred among the cardiacs after delivery than during pregnancy and delivery. The natural way to account for this is that the final effort of labor and delivery is too much for them. But even apparently effortless deliveries as in precipitate deliveries, and where hysterotomies are performed before labor has begun, the cardiac who is in congestive failure is immediately worse, not better. Many suggestions have been made to account for this phenomenon—among them the onset of lactation with increased demand on the circulation, rapid loss of vitamins with lactation, a harmful effect of ergot or pituitary extracts on the heart and circulation, even psychosomatic factors, such as mental letdown after the struggle and excitement of pregnancy and delivery are over. One documented fact must have an effect on the deterioration of the cardiac who is in congestive failure immediately after delivery is that there is an average loss of vital capacity of approximately 250 cc. as soon as the uterus is emptied. The circumference of the thoracic cage becomes smaller. There is also lessening of the intra-abdominal pressure. These factors lessen the stretch of the diaphragm and diminish effective diaphragmatic function. A loss of 250 cc. of vital capacity is little or nothing to the average normal woman or cardiac who has no lung disease and is not in congestive failure. The loss may be critical to a cardiac whose vital capacity has been heavily reduced by congestive heart failure. Other probable factors may be equally or more important: release of pressure on pelvis and leg veins with flooding of the circulation; transfusion of a considerable quantity of blood from the uterus when it contracts following emptying; perhaps in some cases absorption of amniotic fluid with perhaps some pulmonary capillary embolism from particulate matter in the amniotic fluid, such embolism perhaps being particularly troublesome to the patient with pulmonary congestion from heart failure.

Whatever the explanation may be, the fact that even the easiest delivery makes the cardiac in congestive heart failure worse gives emphasis to the need for careful watching through pregnancy in order to anticipate congestive failure by a strict regimen, and leads to a general rule that every effort should be made to improve congestive failure once it has occurred before interrupting a pregnancy. Furthermore, at the Boston Lying-in Hospital we have been led to believe that after the load of pregnancy has once become heavy, it is unwise to interrupt a cardiac's pregnacy before term unless there is some complication such as a severe toxemia which in

itself calls for interruption. Even if the patient is in heart failure which resists medical treatment at the sixth or seventh or eight month, it seems that the chance of successful delivery is greater if we can carry the patient along until the expected lightening of the load in the few weeks before term has become effective. If one delivers a cardiac when the load of pregnancy has grown heavy (roughly after the sixth month) and before the normal lightening of the load during the last few weeks has become effective, one imposes a total load that is greater than the load of delivery at term. We cannot prove by statistics that our cardiacs have done better since the rule, "never interrupt a cardiac for cardiac reasons after the load of pregnacy has once become heavy" has been in effect, but such is our opinion. The infant mortality is much better.

All who are caring for cardiacs in pregnancy should keep the following in mind: Subdivide young women who are cardiacs into "favorable" and "unfavorable" groups before pregnancy. Enlighten the patient before marriage concerning her risk from pregnancy. Let the cardiac and her husband decide if and when they desire to take the risk. If they take it, watch the patient and treat her with more care than one believes is required to forestall congestive heart failure. If failure occurs, diagnose it quickly, treat it vigorously and persistently by medical means. Do not count on interruption of pregnancy to rescue a patient if congestive heart failure appears. It is unlikely to appear before the load of pregnancy becomes heavy. Mortality rates are high if interruption is done at this time for congestive heart failure, so treat the patient by medical means until term when the load of normal pregnancy has lightened and deliver by the easiest method.

Delivery of Cardiacs by Cesarean Section: The rule to avoid premature delivery of cardiacs after the load has once become heavy has reduced the number of cesarean deliveries markedly. In the past, it has been generally believed that cesarean section is the easiest way to deliver the usual severe cardiac, and many still believe this. Fear of sepsis, now largely gone, made routine cesarean delivery for cardiacs distasteful to many. Even so at the Boston Lying-in Hospital, hysterotomies on cardiacs are now done only where there is an obstetrical indication. For the average cardiac are the risks of complications from opening the abdomen, even though the chance for infection is now almost abolished, greater than the risks from delivery through the pelvis? Is the average hysterotomy easier on the circulation than the average delivery from below? No one can answer the questions involved firmly. In any case, the decision is not critical, both methods are well tolerated. In the present state of our knowledge, it seems to me that one is not making a mistake to follow, in general, the conservative plan of not delivering a cardiac by hysterotomy unless there is some obstetrical indication.

The Puerperium: Congestive heart failure rarely appears for the first time in the puerperium, and then only when provoked by some complicating condition such as over-exertion, an embolism, or a fever. Lactation has been feared as a danger to the cardiac. There is an apparent but not yet defined increase in the demands on the circulation during the initial

stages of lactation, and probably a lesser load from continued lactation. So it is the custom to discourage nursing by cardiac mothers. This applies particularly to the more severe cardiacs. Many favorable cardiacs, however, have nursed their babies without apparent harm.

"Idiopathic Myocarditis of Pregnancy and Puerperium": Occasional cases have been reported that have developed symptoms in late pregnancy and in the puerperium that have led some observers to believe that there is an idiopathic myocarditis of pregnancy and puerperium. The case reports that I have read have not clearly established a congestive heart failure nor a myocarditis, but they are striking cases. It is easy to believe that pregnancy had some bearing on the production of the symptoms, though this has not been proven. Perhaps they had a late toxemia. Perhaps they were depleted women whose condition was aggravated by the demands of pregnancy, delivery, and lactation until serious circulatory, renal, and other symptoms appeared. It is certain that cases with unaccountable acute myocarditis during pregnancy-puerperium have been almost unknown in my experience. With economic, social, and medical conditions such as are present in Boston, one need not fear an acute myocarditis in pregnancy or puerperium more than at other times.

Treatment of Congestive Heart Failure in Pregnancy: This is similar in most respects to the treatment of congestive heart failure in general. The well recognized but not yet well-explained tendency for many women to retain fluid in pregnancy is a complicating factor. This edema of pregnancy is not well controlled by any of the usual methods of sodium restriction, etc., and the same can be said for the high circulating blood volume and blood dilution usual in pregnancy. In treating congestive failure in pregnancy, this factor should be recognized and, from my experience, fluid administration of all sorts should be cautiously controlled. It is easier to produce pulmonary edema by forcing fluids of any sort in pregnancy than at other times.

Surgical Treatment of Cardiovascular Defects: To treat or forestall congestive heart failure during pregnancy surgery has been tried. Some successful results have been reported. Data are far too scanty to justify firm principles for these procedures. Decision must be based for each patient on the risk of the operation *versus* the risk of pregnancy without surgical treatment. For example, the risk for "favorable" cardiacs with uncomplicated mitral stenosis (roughly those in Class 1 and 2) for pregnancy, and for surgical treatment of the valve in nonpregnant patients is about the same. The chance for having a live mother and baby at the end of the pregnancy would undoubtedly be lessened if the operation was performed. The same can be said for the unfavorable cardiac with mitral stenosis (Class 3 and 4). The statistical mortality rate for any such operation performed during pregnancy must be lower than the risk of the pregnancy to make surgery an attractive risk. How much lower depends on how much benefit the patient may receive from the operation. Such benefit must be timely —not long delayed—if it is to improve the patient's chance for surviving the pregnancy if she survives the operation. The risk to the child must be considered. So far I have not encountered a pregnant patient with

rheumatic heart disease where the known statistical risks of either surgical treatment or pregnancy *per se* made the surgical treatment attractive to me.

The Surgical Treatment of Patent Ductus Arteriosis: During pregnancy this may well prove to be sound policy. The patient may be promptly cured. The risk of surgery is very small for the mother, much smaller than the risk for pregnancy without surgery in my experience. Clearly, however, the diagnosis should be made before, and suitable treatment given before, not during, pregnancy.

From very scant clinical data now available, and from data suggesting that during pregnancy some rare women have temporarily weakened structure of the aorta, it seems that during pregnancy conditions are not favorable for surgical correction of *coarctation of the aorta*

Mitral Stenosis and "Paroxysmal Dyspnea" in Pregnancy: A small but extremely interesting group of women with uncomplicated mitral stenosis suddenly develop symptoms of severe pulmonary congestion, apparently from acute heart failure. There may be little or no apparent provocation. There are usually rapid heart rate with normal rhythm (even as high as 180) and severe dyspnea with or without asthmatic breathing and/or cough Hemoptysis may occur in any degree, sometimes as a hemorrhage threatening death. There may be pain in the front chest, usually above the heart on the left. Sometimes the pain is severe. Few men with mitral stenosis have these symptoms; more women with mitral stenosis who are not pregnant have them, but it is commonest among women with mitral stenosis who are pregnant. Even among pregnant women with mitral stenosis, only one or two per cent have these violent and paroxysmal "failures." Very few such patients have gone through pregnancy successfully. Most of them have had recurrences of their alarming symptoms in spite of all usual treatment until the pregnancy was interrupted, and then the succession of paroxysms has promptly ceased, though occasional patients have had one or two recurrences shortly after the interruption and then stopped having them From my experience, once a patient with mitral stenosis has had a sudden and violent pulmonary congestion during pregnancy, it is not safe to postpone interruption for a long time. Some have survived a number of repeated "attacks" and then had pregnancy interrupted with excellent results, but a few have died in their second or third attack. I have encountered two patients who had a few comparatively mild attacks during the seventh and eighth calendar months, and none thereafter, who went through delivery successfully, and have done well since. The other patients that I have encountered in pregnancy began their attacks early in pregnancy when it was still feasible to interrupt. Such cases have not yet been adequately followed for expectation for life, but they do not have a good group prognosis. Most of those whose symptoms have appeared in pregnancy and stopped recurring at once after the pregnancy was interrupted have had recurrences months or years later. It is generally believed that surgical treatment of the mitral stenosis is strongly indicated for such patients and it may be that surgical treatment during pregnancy is desirable under

some circumstances; for example, early in pregnancy, where interruption is declined.

Embolism: In spite of all our care and treatment, congestive heart failure is still the single greatest cause of death for cardiacs in pregnancy. Embolism is the next commonest cause (probably in some of these cases congestive heart failure is the main cause of the thrombosis that resulted in death from embolism). In the present state of our knowledge, I have no firm plan for discouraging thrombosis and embolism in cardiacs in the puerperium. Certainly, the need for usual precautions against venous thrombosis is evident. It is not dangerous to get the usual cardiac who is not in failure out of bed early in the puerperium, and the usual simple procedures for keeping the leg veins from undue congestion by "exercise" and suitable pressure bandaging of the legs are safe. In recent years, ligation and division of veins have been freely done in suitable cases. The results have been pleasing. Anticoagulants have not been routinely used by me. They have been used in some of the cases that had vein ligation and division after operation. It certainly is to be hoped that the present active interest in this subject will be sustained and lead to sound methods for reduction of the number of embolic accidents among the cardiacs.

SUBACUTE BACTERIAL ENDOCARDITIS

Before effective antibiotics appeared, subacute bacterial endocarditis caused approximately one-fifth of all the fatalities among the cardiacs in pregnancy. There is nothing about pregnancy to make cardiacs more susceptible to such infections. In fact, some recent statistics show that cardiacs are less likely to have subacute bacterial endocarditis while pregnant than they would be in usual conditions. Delivery and the puerperium, however, offer a chance for infections. In rare cases, it is apparent that symptoms of subacute bacterial endocarditis began shortly after delivery. One must consider whether antibiotics should be given prophylactically. My present plan is to give them after delivery to patients who have aortic regurgitation and to patients who have a history of rheumatic fever and a loud systolic murmur, but do not have mitral stenosis, and continue them until the patient is discharged. I do not give antibiotics to the patients who have uncomplicated mitral stenosis, but give them freely if there is an unexplained, even slight, fever or other symptoms to suggest that there may be an infection. Curiously, careful statistics gathered from large series of patients in several Boston hospitals who died of subacute bacterial endocarditis before the introduction of penicillin treatment have shown that among the married women the chance for contracting subacute bacterial endocarditis appears definitely greater during the three or four months after pregnancy than at any other corresponding interval of time. The high incidence of S.B.E. in the puerperium is not well explained by infections started at delivery and the few days thereafter. One factor appears to be the natural tendency to postpone dentistry during pregnancy and then to have the dentistry, often extractions, in the few months after delivery. It is probably a good plan to take

cultures before a cardiac is discharged from an obstetric clinic. Certainly, blood cultures should be taken if there is the slightest reason to suspect an infection, but this is not enough. Special observation should be continued for the next few months.

Since the introduction of penicillin, it has been shown that patients can survive subacute bacterial endocarditis that is discovered and treated during pregnancy and go through the pregnancy successfully. From replies to questionnaires that I have sent out and from my experience, it appears to me that the death rate is somewhat higher for S.B.E. treated during pregnancy than it is under other conditions; and from observation of individual cases, it seems to me that women with S.B.E. in pregnancy are likely to show more severe symptoms and more evidence of depletion—anemia, even scurvy—than one commonly encounters in the disease in nonpregnant individuals. It is possible that where the disease is recognized early in pregnancy, interruption should be considered. I have never recommended this procedure but believe the question should be considered unanswered until much more data can be obtained. Reports from questionnaires and my own experience indicate that women who have been cured of S.B.E. are not likely to have a recurrence during later pregnancies. Indeed, all such patients that I have heard of and seen have gone through the pregnancy and puerperium without recurrence. A few of these women have had antibiotics throughout the pregnancy and most of them have had antibiotics for a while after delivery. Such women should be advised concerning their risk for pregnancy on the basis of their chronic heart condition alone.

RHEUMATIC FEVER AND PREGNANCY

This subject has interested a number of observers. Others, writing on the heart in pregnancy, ignore it. Those that are interested in the subject usually express and endeavor to support the opinion that active rheumatic carditis is an important factor in prognosis for pregnancy, and occasionally it is suggested that pregnancy is likely to provoke a recurrence or flare-up of rheumatic carditis in susceptible individuals. Some have believed that pregnancy protects against rheumatic fever In my experience, definite rheumatic fever is rare in pregnancy, and also cardiac findings that suggest smoldering or active rheumatic carditis. Postmortem examinations at the Boston Lying-in Hospital have shown no evidence of active carditis in patients with chronic rheumatic heart disease who died suddenly or after a short illness in pregnancy. Slight evidence of activity is usually found in those who died in severe prolonged congestive failure, but in only one case in the last thirty years has active rheumatic carditis appeared at the Boston Lying-in Hospital in the degree commonly found in children with fatal rheumatic fever. The patients with chronic rheumatic heart disease at this hospital averaged twenty-seven to twenty-eight years. Approximately one-fifth of the patients were twenty-two years of age or younger. These younger patients had more recurrences of rheumatic fever than the larger group of older women. Altogether, less than two per cent of my patients have had any clear suggestion of recurrence of rheumatic fever

during pregnancy and in many of these cases, the diagnosis was questionable. Rheumatic fever can occur in pregnancy but it is an unusual event. In my experience it occurs scarcely if any more often in pregnancy or puerperium than in women of comparable age with chronic rheumatic heart disease during a year of living when not pregnant. There are insufficient data at present to indicate interruption of pregnancy for rheumatic fever. Interruption is, for all we know, just as undesirable as allowing the pregnancy to continue. It is, however, certainly not fair to encourage married women with recently active or smoldering rheumatic fever to become pregnant. There are no clear data to guide us in deciding how soon after an attack of rheumatic fever it is advisable to undertake pregnancy. Arbitrarily, one may advise a wait of at least two years. There is reason to believe that adding to the work of the heart has some effect in the development of valvular disease after rheumatic fever, and pregnancy certainly adds to the work of the heart. Since definite data show that recurrences of rheumatic fever are much less likely in women of twenty-three years of age or older than in younger women, it is wise for the young woman who has had rheumatic fever, even though free from it for many years, to postpone pregnancy until she is over twenty-two years of age.

DOES PREGNANCY, IF SURVIVED, SHORTEN THE CARDIAC'S LIFE?

Independent studies of age at death of women with chronic rheumatic heart disease have shown that those who bear children live slightly longer than those who do not. This is a pleasant idea. But individual histories show that some cardiacs enter pregnancy in good condition and are left with larger hearts, and soon thereafter take a fairly rapid downhill course. It is certain that, in general, the heavier the demand on the circulation, the faster the enlargement of the burdened heart chambers, and the greater the likelihood of failure. It is not easy to believe that pregnancy does not hasten the progress of chronic heart disease unless the normal demands of pregnancy have been fully compensated for by careful regimens designed to remove enough work ordinarily done to equal the added work demanded during pregnancy. The unconvincing statistics may be affected by the fact that the worst cardiacs are not so likely to get married and attempt pregnancy as are the cardiacs who are favorable, and less handicapped. The worse the cardiac, the sooner she will die. The better cardiacs live longer and have more time and opportunity for marriage and pregnancy.

A few beliefs that have been expressed on the behavior of cardiacs in pregnancy deserve brief comment: "Cardiacs have easy labor." "Cardiacs miscarry if their hearts fail." "Cardiacs who are in failure or who have auricular fibrillation do not become pregnant." All these statements are false. The last sentence quoted is particularly erroneous. Cardiacs continue to menstruate to almost the same age as normal women and many a cardiac invalid in chronic advanced congestive failure and with established auricular fibrillation has become pregnant.

ESSENTIAL HYPERTENSION

Because of the difficulty during pregnancy of distinguishing between the toxemias of pregnancy, essential hypertension, and hypertension associated with nephritis, and the fact that patients with hypertension are often seen by an obstetrician or cardiologist only after they have become pregnant, adequate data on the prognosis and treatment of uncomplicated essential hypertension in pregnancy are lacking. Furthermore, the difficulties in subdividing known individuals with essential hypertension into varying degrees of severity have not yet been overcome. It appears, from my experience at the Boston Lying-in Hospital, and with private patients, that patients with mild degrees of essential hypertension are approximately as common among pregnant women as are patients with rheumatic heart disease. The maternal death rate is not quite as high among the mild hypertensives as it is among the "favorable" cardiacs. There is, however, a heavy maternal death rate for the patients who have severe hypertension and those who with their hypertension have evidence of cardiac enlargement and myocardial change or symptoms of circulatory embarrassment. The death rate among such cases is comparable to the death rate among the unfavorable cardiacs. Furthermore, there is a belief, not fully supported but held by many observers including myself, that pregnancy tends to accelerate the progress of essential hypertension.

The hypertensive patient who elects pregnancy should be guarded by the same general rules that apply to the patient with chronic rheumatic heart disease. Obstetrician and cardiologist should work even more closely together. The difficulty in assessing the symptoms of toxemia and hypertension are so great that the experienced obstetrician must keep in close touch with the patient, particularly in the last trimester. In hypertension, with or without toxemia, it seems that an essential point in treatment of mother and fetus is to decide if and when pregnancy should be terminated. The rule, "Do not interrupt pregnancy when the load has once become heavy before term for cardiac reasons," does not apply to the hypertensive patient. This whole subject needs more study and documentation as, of course, does hypertension in general.

Management of hypertension is much the same as under usual conditions though closer watch on the possible effect of severe sodium and protein restriction is clearly indicated and undoubtedly closer control of all the stresses known to affect hypertension are needed than if the patient did not have the stress of pregnancy itself. The importance of the hypertensive albuminuria in pregnancy in the prognosis of women after successful delivery was shown years ago when a very large series followed for a number of years had a mortality rate several times that of normal expectancy.

Though the vast majority of cardiacs who become pregnant have rheumatic heart disease, nearly all of the cardiac diseases discussed in these volumes may occur in a pregnant woman. For example, pregnancy complicated by each of the following and many other rare cardiovascular diseases, have been discussed in the literature: Complete dissection of the aorta, complete heart block, cardiovascular chances associated with

kyphoscoliosis, atresia of the aorta, pregnancy in patient with Wolff-Parkinson-White syndrome. When one encounters such and other rare situations, one must consult the special literature or seek the specially informed consultant. Such rarities cannot be feasibly covered adequately in volumes devoted to the whole field of cardiovascular disease such as this. This statement also applies to pregnancy in women with congenital cardiovascular malformations.

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WILLIAM B. PORTER, M.D.
AND
RENO R. PORTER, M.D.

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Acute Pericarditis

Definition: Acute pericarditis is an acute inflammatory process involving the parietal and visceral layers of the pericardium. Except for the nonspecific (benign) type, it is always found in association with a systemic disease, a septicemia, or an inflammation in contiguous tissues, and, as such, should not be considered an independent entity but rather a complication or extension of the underlying disease process.

Etiology and Classifications: Acute pericarditis is due to a variety of infectious agents, as well as several noninfectious causes. It results in two basic types of reaction. One consists of a fibrinous or serofibrinous exudate *with minimal to absent fluid (pericarditis sicca), while the other consists* of a fibrinous, serosanguinous, or purulent exudation, with the accumulation of an appreciable quantity of fluid in the pericardial sac which may, in itself, become of clinical significance (pericarditis with effusion). For this reason, acute pericarditis has been classified, at times, according to the nature of this reaction and whether or not an effusion is present. However, the specific etiologic agent is largely responsible for the severity and character of the pericardial reaction and is the determining factor in prognosis and treatment. It is highly desirable, therefore, to have, as a basis for the approach to the clinical problems of acute pericarditis, a classification of a different order from that which is founded upon the nature of the pericardial inflammatory reaction.

The following classification gives one the proper perspective since the type of pericarditis is immediately related to the associated disease or causative factor and this orientation logically suggests a concise and rational foundation for prognosis and treatment:

A. Rheumatic pericarditis (rheumatic fever).
B. Acute nonspecific (benign) pericarditis
C. Bacterial pericarditis:
    (a) Tuberculous pericarditis
    (b) Pyogenic (purulent) pericarditis
D. Nonbacterial:
    (a) Myomalacic pericarditis (myocardial infarction).
    (b) Uremic pericarditis.
E. Traumatic pericarditis.

There are other forms of acute pericarditis which are quite rare and deserve only to be mentioned in passing. These include pericarditis asso-

ciated with disseminated lupus erythematosus and with infectious mononucleosis, cholesterol pericarditis, chylopericardium, and infections due to echinococcus and fungus.

Pathology: Acute pericarditis begins as a localized inflammatory or a noninflammatory fibrinous reaction of the pericardium. It may remain localized and confined to one layer of the pericardium. Usually, it soon spreads over the entire surface of the heart and involves both layers of the pericardium. In many types of acute pericarditis, the inflammatory reaction extends down into the subepicardial myocardium. Varying amounts of serous, hemorrhagic, and/or purulent effusions may be formed, the quantity varying from a few cc. to as many as 3000 cc. Localized effusions occasionally occur. One of the writers (W.B.P.) has observed a patient with tuberculous pericarditis who had an effusion localized over the right auricle and part of the right ventricle. The roentgenogram had many features suggesting a large aortic aneurysm, and the clinical picture was quite similar to the syndrome of constrictive pericarditis.

Symptoms: Acute pericarditis may exist without the addition of any subjective complaints distinct from those associated with the primary disease; but there are two circumstances which give rise to new symptoms.

The first of these is the inflammatory involvement of the parietal pericardium, particularly that which is contiguous to the pleura, diaphragm, or anterior mediastinum. This gives rise to chest pain which is usually sharp and knifelike in character and may be intermittent or continuous. It varies in intensity from mild to severe and is frequently aggravated by respiration and other movements of the chest wall. The area of distribution is variable, being, at times, only remotely related to the precordial area. It is located most frequently over the lower sternal region or along the left sternal border. At times, the pain radiates to or is localized to the upper abdomen, the left shoulder, and the left scapular area posteriorly. It is an interesting observation that in myomalacic and uremic pericarditis, where the process is confined within the pericardial sac, pain is never a symptom.

The second circumstance that accounts for symptoms is the development of a significant degree of pericardial effusion. This results in two sets of symptoms, those resulting from an increase in intrapericardial pressure and those due to the compression of adjacent structures by the distended pericardial sac. The first of these effects is dependent upon the rate of formation and the quantity of the effusion. A small effusion may produce no symptoms, whereas a moderately large effusion (500 cc; 1 pint), which has accumulated rapidly, seriously interferes with cardiac filling (cardiac tamponade). This produces a combination of venous engorgement ("backward failure") and diminished cardiac output ("forward failure"). Venous engorgement leads to right upper quadrant pain from distension of the liver, and to varying degrees of edema of the feet and legs. The diminished cardiac output causes weakness and faintness. Dyspnea and orthopnea may also be present, but these are related, more often, to the fact that respirations are painful, giving rise to rapid, shallow respiratory movements. Large effusions produce these symptoms in

greater degree and, in addition, produce symptoms of extrapericardial compression, such as cough, cyanosis, dysphagia, and hoarseness. The clinical picture in patients having large effusions may masquerade that of advanced congestive heart failure. The similarity of these symptoms and altered circulatory dynamics to those occurring in congestive heart failure may lead to the erroneous diagnosis of primary myocardial insufficiency.

Physical Signs: The physical findings associated with acute pericarditis are those phenomena caused by the fibrinous exudate and by the accumulation in the pericardial sac of an effusion sufficient in quantity to be clinically detectable.

A to-and-fro *friction rub* over the precordial area is a characteristic finding and is sufficient evidence to warrant the diagnosis of pericarditis. It is a scratchy, superficial sound, often quite faint, and must be looked for with diligence and concentration. It is heard with greatest intensity during held expiration, and may be audible only at this time. This finding is more readily noted if the chest piece of the stethoscope is applied with moderate pressure and particularly so, if the chest piece is of the diaphragm type. It must be searched for at frequent intervals, for often it is evanescent and can be heard for only a brief time during the course of the disease. This sign may be mistaken for an endocardial to-and-fro murmur, and *vice versa*, but this error in interpretation is not probable if due consideration is given to the established points in differential diagnosis. The presence of a pericardial friction rub does not negate the existence of a significant degree of pericardial effusion. The heart tends to fill the space between the sternum and spine, and will remain against the anterior parietal pericardial sac even in the presence of large effusions.[9] A pericardial friction signifies pericarditis, which implies that a large effusion may be either in the making or is actually present.

The physical phenomena which are caused by the accumulation of fluid in the pericardial sac can be divided into two groups, those which are the result of the enlarged pericardial sac and those which result from cardiac tamponade.

Signs of an Enlarged Pericardial Sac: 1. An increase in the supracardiac dulness in the second and third interspaces, especially to the left of the sternum, is an early sign of effusion. This is elicited by light percussion with the patient in a recumbent position. It will be noted that the extent of the dulness lessens or disappears when the patient sits up. There is a high area of left auricular dulness and an increased area of absolute cardiac dulness. The left border of cardiac dulness is found to extend beyond the apical impulse, if this latter is discernible.

2. The heart sounds are diminished in intensity and the apical impulse is less readily seen and felt.

3. There are evidences of consolidation or atelectasis in the lower lobe of the left lung (Ewart's sign). These posterior phenomena assume one of two rather distinct types. (a) Distant bronchial breathing and impaired resonance are noted at the angle of the left scapula. With large pericardial effusions, these findings increase to involve the entire left lower lobe

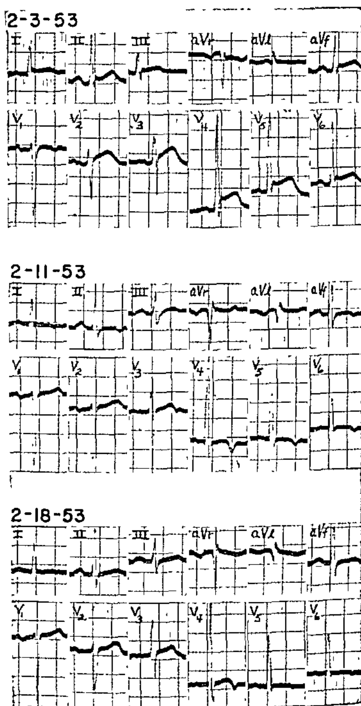


FIGURE 1. Electrocardiogram Case of acute nonspecific pericarditis.

posteriorly, closely imitating a pneumonic consolidation. (b) There are the physical phenomena of pulmonary consolidation plus those of a pleural effusion. These findings, at times, are so strikingly similar to those produced by a pleural effusion, that occasionally a pericardial sac is aspirated posteriorly under the mistaken belief that it is a pleural effusion. It is obligatory, therefore, that some distinctive differential point be found to aid in the clinical separation of pericardial effusion and pleural effusion when these elusive phenomena are present. It will be noted that the upper margin of percussion dulness in patients with pericardial effusion reaches its maximum height at the angle of the scapula, descends downward in the axilla, reaching the lowest point in the mid-axillary line, then rises to become continuous with the left margin of cardiac dulness. An analysis of this line of dulness shows it to be a reverse of the Ellis' "S" shaped line observed in pleural effusion. The major difference is the absence of axillary flatness consistently found in pleural effusions. The inverted "S" line has proven to be invaluable in differentiating pericardial effusion from pleural effusion when other confusing phenomena existed over the area of the left lower lung.

Signs of Cardiac Tamponade: 1. A pericardial effusion, depending upon its volume and the rapidity of its development, may interfere with cardiac filling and produce an inflow obstruction. This causes a rise in venous pressure, resulting in distension of the neck veins above the level of the right auricle, an enlarged and tender liver, and, if this state continues, widespread edema and ascites

2. The interference with cardiac filling also causes a reduction in cardiac output and there results a fall in systolic and pulse pressure and an increase in heart rate.

3. Pulsus paradoxus occurs and is recognized by a significant decrease in pulse volume (and systolic blood pressure as noted on the sphygmomanometer) during inspiration This is a reversal of the normal respiratory variations of the pulse which consist of an increase during inspiration and a decrease during expiration This phenomenon also occurs in other cardiac and pulmonary diseases, and this fact greatly lessens its diagnostic significance.

Electrocardiogram: The characteristic changes which occur in the electrocardiogram (Fig. 1) consist of an initial slight elevation of the S-T segment, which persists for several days to a week or more. Gradually the S-T segments return to the isoelectric line, concomitant with the development of low, flat, or slight to moderately inverted T waves. These changes may be present in only a few leads, or in as many as ten leads of the routine twelve-lead electrocardiogram The reciprocal elevation of the S-T segments (except sometimes in aVr) and the Q waves changes which are characteristic of myocardial infarction are not seen. In most instances the electrocardiographic changes return to normal after several weeks, although some abnormalities persist indefinitely. The deviations occurring in the electrocardiogram have been attributed to reduction in coronary blood flow resulting from the pressure effects of the pericardial effusion on the coronary circulation. However, the withdrawal of peri-

cardial fluid does not alter these changes in the electrocardiogram, a fact which indicates that the intrapericardial pressure is not concerned in the pathogenesis of the electrocardiographic abnormalities. It is generally agreed now that the observed changes occurring in acute pericarditis are due to involvement of the subepicardial myocardium by the inflammatory reaction in the pericardium.[5]

Roentgenography: Roentgenographic examination of the heart in acute pericarditis reveals no significant findings unless an effusion is present, under which circumstances there often are characteristic findings, which may be extremely helpful in diagnosis. Teleoroentgenograms show enlargement of the cardiac silhouette, the degree depending upon the

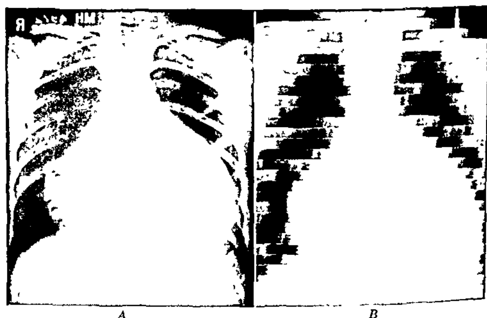


FIGURE 2 *A* Teleoroentgenogram. *B*. Kymographic teleoroentgenogram Case of tuberculous pericarditis with effusion.

amount of effusion. The characteristic change is a "waterbottle" appearance to the cardiac shadow, which is narrow in the superior portion and rounded and wide in the lower portion (Fig. 2*A*). The roentgenograms should, if possible, be made in both the recumbent and sitting positions since this will demonstrate the changes in shape resulting from the effect of altered posture on the distribution of the pericardial effusion.

The fluoroscope is useful in determining the size and shape of the cardiac shadow, but, in addition, is particularly valuable for studying the amplitude of cardiac contraction, which progressively decreases as the quantity of pericardial fluid increases. This finding, at times, may be so marked that no pulsations are seen and a picture approaching a "dead heart" results.

The kymograph (Fig. 2*B*) is another means for studying the amplitude and character of the heart's contracting waves. It is doubtful whether it

gives more data than a careful fluoroscopic study, except that a permanent record of the motions of the heart border is obtained.

Roentgenographic studies done after aspiration of fluid and the injection of 100 to 150 cc. of air (Fig. 3 *A* and *B*) is often quite revealing and gives additional useful information. The size and shape of the heart, the presence or absence of tumor masses, and the thickness of the pericardium can be determined by this means.

Other Findings: Fever, leukocytosis, and an elevated sedimentation rate occur in acute pericarditis. Where the pericarditis is a part of some other disease process, these changes conform, in general, to those associ-

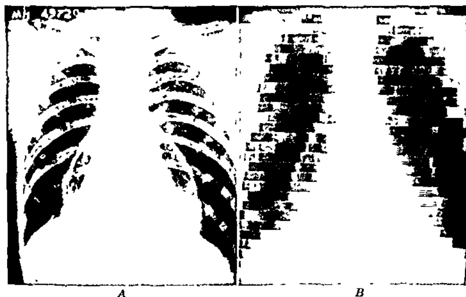


FIGURE 3 *A* Teleoroentgenogram *B* Kymographic teleoroentgenogram. Same case as Fig 2, following aspiration and the introduction of 300 cc of air

ated with the primary disease and are not materially altered in degree or character by the additional inflammatory reaction in the pericardium. Nonspecific pericarditis, which usually follows a previous upper respiratory infection, has fever, leukocytosis, and an elevated sedimentation rate as the initial features of its onset. Tuberculosis of the pericardium is likewise distinctive, for a moderate leukocytosis is usual in serous membrane tuberculosis, whereas the leukocytosis is slight, if any, in uncomplicated pulmonary or glandular tuberculosis.

Differential Diagnosis: The pericardial friction rub may be confused with *endocardial murmurs*, but this is rarely a problem in differential diagnosis, if careful attention is paid to the auscultatory findings. Occasionally, the diastolic murmur of aortic or pulmonic insufficiency, which is heard quite well along the left sternal border, may resemble the diastolic component of a pericardial friction rub. Usually, however, this murmur is soft and blowing and does not have the superficial scratchy characteris-

tics of a friction rub. Further, any systolic murmur associated with such a diastolic murmur generally is quite harsh and is definitely lower in pitch, and bears no similarity to the systolic component of a friction rub.

The combination of signs and symptoms of venous congestion with findings suggesting enlargement of the heart may present some diagnostic difficulties between pericarditis with effusion and *congestive heart failure* on the basis of myocardial and/or endocardial disease. Cardiac dilatation and pericardial effusion do, at times, have a superficial similarity. The history of the illness is most helpful in this differentiation, for the causes of myocardial failure are distinctive and quite different from those occurring in patients with acute pericarditis. The presence of a gallop rhythm and more distinct heart sounds distinguish myocardial failure from pericardial effusion. Likewise, careful comparison of the findings of palpation and percussion will indicate that the left border of cardiac dulness extends beyond the apical impulse in pericardial effusion. The circulation time (arm-to-tongue) has been reported by Bellet *et al.* (1951) to be normal or only slightly prolonged in pericardial effusion and, therefore, useful as a differential finding from cardiac dilatation where the circulation time is always prolonged This appears to be a helpful differential point, but in our experience, is not specifically diagnostic in all cases. Fluoroscopic examination of the heart generally is most helpful since the amplitude of cardiac contractions are much less, and may be entirely absent, in pericardial effusion as compared to those seen in a dilated heart. This is not invariably so because, in some instances, a tremendously dilated heart may have very feeble or imperceptible pulsations of the cardiac borders. Rarely, a diagnostic pericardial tap may be required to make the differentiation We have had the experience recently of following a patient for many months with the diagnosis of idiopathic cardiac hypertrophy and fibrosis until someone had sufficient doubt as to the correctness of the diagnosis to do a pericardial tap, which revealed a large pericardial effusion. Angiocardiography is very helpful in the differential diagnosis since it will demonstrate the small heart chambers in the larger area of pericardial effusion. However, this is a somewhat formidable procedure and should be used in only the difficult situations where differentiation is of critical importance to the patient and cannot be made by other means.

The differentiation of *coronary occlusion* with myocardial infarction from acute pericarditis, particularly the nonspecific type, has been receiving increasing attention in recent years. The sudden onset of substernal pain may suggest a myocardial infarction and, in occasional instances, the differentiation may not be apparent for several days or more. In the typical case, the sharp character of the pain with its restrictions on respiration, the presence of a friction rub, fever, leukocytosis, and elevated sedimentation rate on the first day of illness, and the electrocardiographic findings, serve to identify the episode as acute pericarditis rather than acute myocardial infarction.

Primary or secondary *tumors* of the pericardium may give rise to pericardial effusions and other phenomena suggesting acute pericarditis. The history is usually quite helpful in making this differentiation. The aspi-

rated pericardial fluid is nearly always hemorrhagic and may contain tumor cells when suitably stained. X-rays taken after withdrawal of fluid and injection of air into the pericardial sac frequently demonstrate the tumor mass. In some instances, pericardial exploration and biopsy may be necessary.

Acute pericarditis, at times, is accompanied by very confusing abdominal symptoms, simulating so perfectly some acute *intra-abdominal pathology*, that useless operations for suspected surgical diseases have been done. This is particularly true of nonspecific pericarditis, where abdominal pain and tenderness may be the only symptoms for the first few days. This error will be avoided if due consideration is given to the entire clinical history and to a careful examination of the heart.[12]

Treatment: The specific treatment of acute pericarditis varies with the etiological nature of the disease. When it occurs during the course of any primary disorder, it may or may not require additions to or modifications of the therapeutic regimen already instituted (see Specific Types of Acute Pericarditis).

Regardless of the type of pericarditis, thoracic distress and pain are prominent symptoms and require therapeutic control. A lightly filled ice-cap placed over the precordium frequently gives considerable comfort and should be tried routinely. As a rule, the use of opiates is indicated and required. These not only relieve pain, but promote sleep and lessen the patient's anxiety, which at times, is most distressing.

Pericardial Paracentesis: When pericardial effusion is of sufficient degree to cause cardiac tamponade or serious compression of lung tissue, pericardial paracentesis must be done promptly to relieve the circulatory embarrassment and/or respiratory distress. There are several sites at which pericardial taps can be made. The apical and subxyphoid are the ones most commonly used, with the parasternal routes and the posterior thorax route employed less frequently.[7] The site selected should be the one most suitable for the particular patient as determined by careful study of the patient, including PA and oblique chest x-rays and cardiac fluoroscopy. It will be found that just within the outer border of cardiac dulness (1 to 2 cm. outside of the apex impulse, if perceptible) in the fifth or fourth intercostal space (apical approach) is the area of choice in the majority of patients. The second commonest choice is the point formed by the junction of the ensiform process and the left costal arch (subxyphoid approach). In this approach, the patient's body should be elevated thirty to forty degrees and the needle directed slightly upward. This site is particularly useful when there is a large effusion, which tends to recur rapidly, and it is desirable to empty the lower part of the pericardial sac. It is also the route of choice in instances where the amount of fluid is considered to be slight or questionable. When the effusion projects unusually far to the right, the needle may be inserted in the fourth intercostal space 1 cm. to the right of the sternum. In the rare case where fluid is not obtained from the anterior sites and there are well developed posterior compression phenomena (Ewart's sign), the posterior thoracic approach can be utilized. The needle is inserted in the seventh or eighth

intercostal space in the midscapular line, with the left arm raised to lift the scapula upward and outward from the site of puncture. This site for paracentesis should not be chosen if purulent pericarditis is suspected, for the danger of pleural infection by the contaminated needle is great.

The site selected for the puncture should be anesthetized adequately with a local anesthetic (two per cent procaine). It is desirable to use a No. 27 needle to infiltrate the skin and chest wall, including the pleura and sufficient time must be allowed for the anesthetic to take effect before the exploratory needle is inserted. If the patient is distressed by pain, breathlessness, and anxiety, the procedure should be preceded by an *opiate* administered hypodermically. The patient should be placed in a sitting or semisitting position. The aspirating needle should be either No. 20 to No. 18 gauge and have a short bevel. A 30 cc. glass syringe is a convenient size, which is attached to the needle by a piece of rubber tubing, 4 cm. in length, which allows some movement of the needle if it comes in contact with the heart.

Regardless of care used, the heart is occasionally felt against the trocar, and the ventricular wall may even be perforated without harm, but injury to a coronary artery may be serious. This fact emphasizes the importance of assuring a patent lumen by the use of a stilet and the choice of a needle with a short-beveled point.

SPECIFIC TYPES OF ACUTE PERICARDITIS

Rheumatic Pericarditis. ***Pathology:*** Rheumatic pericarditis is a part of the carditis that may occur during the course of active rheumatic fever. It is doubtful if it ever is present as an isolated rheumatic lesion, or, at least, it would be most uncommon for it to be recognized as such. It consists of a fibrinous or serofibrinous inflammatory reaction involving the entire pericardium. The cellular exudate is made up of plasma cells and lymphocytes and usually extends into the subepicardial tissues. The mass of fibrin may be quite dense and firmly adherent to the serous surfaces Typical Aschoff bodies are seen at times and, when present, are diagnostic, but their absence does not exclude the rheumatic nature of this type of pericarditis A small or moderate amount of fluid may be found between the fibrinous adhesions, sometimes definitely loculated. On occasions, there may be an appreciable quantity of fluid free in the pericardial cavity as a definite effusion. This fluid is serous in most cases, but may be serosanguineous, particularly in fulminating cases.

Clinical Features: The clinical behavior of rheumatic fever is no index to the probability of pericarditis. Rheumatic pericarditis is not unusual in patients in whom the other manifestations of the disease are so mild that they are entirely ignored by the individual, but, generally, it is seen in patients rather acutely ill with active rheumatic fever. Thomas *et al* [15] have emphasized the differences in the clinical features and prognosis of rheumatic pericarditis with an effusion from that without an effusion. The latter is a relatively unimportant early manifestation of active carditis, whereas the former occurs later on in the course of rheumatic fever and

is much more serious in its implications. A pericardial friction rub is the characteristic finding. There may be no other alterations in the clinical course of the rheumatic fever although, at times, there is an associated increase in many or all the evidences of active disease. Significant amounts of pericardial effusion commonly are present but the quantity is not clinically detectable since, ordinarily, it is impossible to determine how much is effusion and how much is cardiac dilatation secondary to the rheumatic myocarditis. This problem does not introduce serious difficulties for the reason that it is doubtful whether one is ever justified in assuming that effusion accompanying rheumatic pericarditis is of sufficient degree to require aspiration

Treatment: The occurrence of acute pericarditis as a complication during the course of acute rheumatic fever is a somewhat ominous development and requires an intensification of the therapeutic regimens already instituted, whether salicylates, antibiotics, and/or adrenal steroids. It is an indication that the underlying disease is still quite active or that a recrudescence has occurred. It generally responds very well to adrenal steroids, and these should be given or reinstituted if they have been discontinued previously.

Acute Non-Specific (Benign) Pericarditis. ***Pathology:*** The pathology of this condition is not known too well because the disease, in practically all cases, runs a benign course without fatality, and postmortem studies, therefore, are scanty. It is considered to be a serofibrinous type of inflammatory reaction, infectious in nature, and probably viral in origin. The amount of pleural effusion is usually small and, in the majority of those instances where aspiration was done, has been found to be serosanguinous.[11]

Clinical Features: This condition is generally considered to be a benign, self-limiting disease, lasting one to three weeks from which recovery is complete and without significant sequelae[2] However, in a recent report of twenty-four cases of benign pericarditis,[3] two cases later developed constrictive pericarditis, which required pericardial resection six and twenty months following the acute episode It is more commonly encountered in adults, but cases have been reported in the pediatric age group.[4] The disease begins during or following a nonspecific respiratory infection with the rather sudden onset of chest pain and fever. The character of the pain varies from patient to patient, being described as "sharp," "knife-like," sometimes "dull," and occasionally as "crushing." The intensity varies, but is always sufficient to require medication for relief. The commonest location of the pain is along the left sternal border or over the lower sternal area, but, at times, it is noted in the epigastric area and less frequently over the precordium and in the left shoulder. Associated with this pain, there is sometimes felt a deep substernal soreness similar to that felt after physical injury to the sternum. Both the pain and soreness are aggravated by respiration, cough, and other movements of the chest. The pain is a much more consistent and significant symptom in nonspecific pericarditis than in other types of acute pericarditis. The pain gradually diminishes in intensity over a period of several days to a week.

A pericardial friction rub, sometimes lasting for many days, is the most significant physical phenomenon. In one of our cases the friction rub was present for twelve days. Pericardial effusion does not occur in amounts sufficient to be detected on physical examination. Teleoroentgenograms have shown an increase in the size of the cardiac silhouette at the onset of the disease and a reduction in size following recovery. This has been attributed by some writers to cardiac dilation[6] but it is the authors' opinion that this is due to pericardial effusion alone. Recurrences, apparently, are quite common, occurring in thirty per cent of the cases reported by Tomlin, Logue, and Hurst.[14]

There have been reports of fatalities in this type of pericarditis from the use of anticoagulant drugs, in the mistaken belief that the patient had an acute myocardial infarction. Death was due to extensive hemopericardium. This points out the importance of differentiating this disorder from myocardial infarction (see Differential Diagnosis).

Treatment: Therapy is essentially symptomatic in nature since the disease is self-limiting It has not been demonstrated that antibiotics are of any particular value, but, in view of the probable viral etiology, it seems wise to undertake some type of specific therapy. At the present time, tetracycline, 0.5 Gm. four times daily for a period of ten days to two weeks, seems the preferable therapeutic agent. The adrenal steroids have been used in the treatment of this condition with dramatic improvement reported[4] It seems doubtful that such therapy is indicated in the average case, although its use might be considered if the course is unusually acute or unduly prolonged.

Tuberculous Pericarditis. ***Pathology:*** Tuberculous pericarditis is an inflammatory reaction of the pericardium showing characteristic tubercles, epithelioid cells, subsequent hyalinizing fibrosis, and scattered giant cells. The myocardium and immediate epicardial layer of fat are rarely, if ever, involved, although encapsulated tubercles are occasionally found in the myocardium. The epicardial fat layer is often thick. The actively granulating outer surface of inflammatory tissue, which is vascular and in which fibroblasts are proliferating, greatly favors the formation of adhesions, which may become generalized and dense.

Clinical Features: Tuberculous pericarditis occurs more often by the direct spread of infection from caseous mediastinal lymph glands or from clinically quiescent pleural or pulmonary foci. Occasionally it is a part of multiple serous membrane tuberculosis or of miliary tuberculosis. The clinical course is both elusive and variable, and the condition, therefore, is frequently confused with other diseases. It is a serious disease, yet, many cases do go unrecognized and recover with slight disability. The diagnosis is made on the basis of the clinical history, x-ray studies, and from bacteriologic examination of the aspirated fluid. In those instances where the bacteriologic results are negative, a presumptive diagnosis can be made on the history and course of the disease and the demonstration of a thickened parietal pericardium as seen on chest x-rays taken after injection of air into the pericardium. Those cases presenting the symptoms and signs of massive pericardial effusion may be confused with heart failure

when prolonged subacute tamponade has resulted in extensive e enlarged liver, and venous congestion, yet, the probability of en remote if reasonable care is exercised.

Treatment: The treatment of tuberculous pericarditis is an indiv problem. In all cases, however, the established therapeutic principl active tuberculosis must be rigidly adhered to in an effort to arres active lesions. Effusions, when they occur, are usually quite large repeated aspirations may be required. While there is some merit i injection of air into the pericardial sac after aspiration of fluid, at from a diagnostic point of view, there appears to be considerable that this is of any therapeutic value, as was thought earlier.

The introduction of the antimicrobial agents, particularly those eff against the tubercle bacillus, has altered the therapeutic approa tuberculous pericarditis, and has modified, to a considerable extent clinical course and ultimate outcome of such diseases. The manage with these newer agents has not been definitely established, and is s the exploratory phase. There is no question as to their efficacy, bu problems of preferable drug and proper dosage remain to be se Streptomycin alone has been used to some extent[3, 10] and with good re but a more recent agent, isoniazid appears to be the drug of choice, it has the best penetration and is more likely to reach the deeps tubercle bacilli in a pericardial exudate. The recommended dose is 10 three times daily. In addition, it appears advisable to supplement drug with either streptomycin 0.5 Gm. twice weekly or para-aminosali acid 3.0 Gm. four times daily. The general trend is for prolonged treatment of tuberculosis, so therapy should be continued for a peri twelve to eighteen months, irrespective of the fact that laboratory other evidences of activity subside prior to this. This therapy ca continued on an ambulatory basis at home, after the initial acute m festations have subsided It remains to be seen how this therapy alter the course of this disease, and, particularly, how it will modify chronic changes we have expected in the past.

Pyogenic Pericarditis. *Pathology:* Pyogenic pericarditis is due commonly to the pneumococcus or staphylococcus, less frequently t streptococcus, and rarely to colon bacillus, gonococcus, *Bacillus melit Bacillus tularensis*, and *Bacillus influenzae*. Except for infection follo direct trauma, it is always secondary to a pyemia elsewhere in the b It occurs most commonly from direct extension of an adjacent i thoracic inflammatory process, such as purulent foci in the lung mediastinum. It is due, less frequently, to a bacteremia, as occu acute bacterial endocarditis or in a metastatic invasion from a dis focus such as osteomyelitis. It may be a localized or generalized pur inflammation of the pericardial sac, with, generally, some infiltration the adjacent myocardium. There is a small to moderate amount of p lent fluid which varies in consistency from thin to quite thick.

Clinical Features: Pyogenic pericarditis is seen less frequently probably due to the widespread use of the newer antibiotic drugs, w

give rise to secondary invasion of the pericardium. As in other forms of acute pericarditis, the onset may not cause any symptoms in addition to those peculiar to the disease, of which it is a complication. However, when a patient suffering with acute osteomyelitis, emphysema, pulmonary suppuration, or suppurative peritonitis continues to be ill in spite of adequate therapy, purulent pericarditis should be looked for as a possible complication The development of precordial distress and breathlessness along with the symptoms of sepsis demands a careful search for the physical phenomena of pericardial disease. There are diverse opinions as to the relative value or danger of a diagnostic pericardial paracentesis in suspected pyopericardium. Except for surgical pericardiostomy, it is the only way to make a correct diagnosis and obtain material for sensitivity studies, both of which are extremely important if treatment is to be successful. If properly performed, the implied dangers are unimportant in comparison with the value of the procedure. As far as possible, aspiration through normal lung tissue should be avoided.

Treatment: Every effort must be made to determine the existence of purulent effusion at the earliest possible moment by the use of a diagnostic pericardial puncture. Culture of the fluid obtained and determination of the organism responsible and its sensitivity is necessary for determining the proper antibiotic therapy to be instituted. In general, the dosage should be massive and continued for about two weeks after all evidences of active infections have subsided. Pneumococcus and staphylococcus organisms are the ones most commonly encountered. If pneumococcic infection is suspected at the time of the initial diagnostic tap, 50,000 units of penicillin can be instilled into the pericardial cavity. In addition, penicillin in large amounts, one to two and a half million units every three hours, should be administered. If staphylococcus, or other organisms, are the offending organisms, sensitivity studies are mandatory in order to determine which agent will be effective. Use the two drugs found to be most effective, most likely penicillin, one to two and a half million units every three hours, erythromycin 4.0 Gm. daily, and/or chloramphenicol 4.0 Gm. daily.

The need for surgical pericardiostomy and drainage as treatment seems less imperative now that satisfactory antimicrobial agents are available. Experience has been too limited to draw any final conclusions, but it seems probable that surgical treatment in the acute stage can be dispensed with if early and adequate antibiotic therapy is instituted.

Uremic Pericarditis: Uremic pericarditis is a noninflammatory fibrinouslike exudate over the surface of the pericardium which occurs during the terminal stages of renal failure from glomerulonephritis, nephrosclerosis, and pyelonephritis. It does not take the characteristic fibrin stains and histologically it has the characteristics of a protein precipitate. There is no involvement of the underlying myocardium. It is never associated with an effusion unless it becomes secondarily infected. Uremic pericarditis does not justify more than casual consideration in a discussion of acute pericarditis, for it is not infectious in origin and in no way alters the clinical course of the primary disease. It is considered an ominous prog-

nostic sign so far as the renal failure is concerned. No particular therapy is indicated.

Myomalacic Pericarditis: It is probable that whenever a patch of myomalacia (myocardial infarction and/or degeneration) occurs at or near the surface zone of the myocardium, there develops a mild, localized, fibrinous, inflammatory reaction involving the adjacent epicardium. This process is characterized by some edema, a mild round cell infiltration, and some engorgement of the small capillaries in the epicardium. This process *tends to spread laterally and may involve a larger area of epicardium* than is represented by the underlying myomalacic patch. It has no clinical significance, other than indicating the presence of a subepicardial myocardial infarction, and no specific treatment is required

In this connection, however, it is well to point out the possibility of hemorrhagic pericarditis secondary to hypoprothrombinemia occurring during the course of anticoagulant therapy in myocardial infarction.[15] The pericarditis of uncomplicated myocardial infarction is of brief duration. A persisting pericardial friction rub or the appearance of such a sound after the second week of the disease in a patient on anticoagulant therapy should make one suspicious of a complicating hemorrhagic pericarditis. Evidences of the development of a pericardial effusion makes such a diagnosis almost certain in a patient on anticoagulant drugs who shows a significant depression of the prothrombin activity. This condition should be kept in mind as a possible complication in the course of anticoagulant treatment of myocardial infarction. Early recognition is imperative, since it may prove fatal if corrective therapeutic measures are not instituted promptly.

Traumatic Pericarditis: Traumatic pericarditis occurs as the result of a penetrating wound of the pericardium and, in a few instances, from a nonpenetrating blow to the anterior chest. A fibrinous exudate and hemopericardium develop as a result of contusion and laceration of the pericardium, rupture of a coronary vessel, or from perforation of the heart wall. The clinical features are those of pericarditis, with or without an effusion, occurring in a patient giving a history of a prior chest injury. The hemopericardium may be of sufficient degree to cause tamponade of the heart, which should be treated by repeated aspirations, as needed. In the absence of tamponade, it seems wise to aspirate as much of the effusion as possible since there is some evidence to indicate that the hemopericardium may become organized and fibrotic and lead to constrictive pericarditis. This can be done quite adequately by needle aspiration in the vast majority of cases, but, occasionally, surgical pericardiostomy will be needed.

In penetrating pericardial wounds, where there is contamination with pyogenic organisms, a purulent pericarditis will be superimposed on the hemopericardium. This is treated in a similar fashion to other forms of pyogenic pericarditis.

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Chronic Constrictive Pericarditis*

Introduction: Preparation for a new edition of this work has enabled me to review with my associates, in particular Dr. John C. Dalton, the new cases and experience that we have had since the last edition which presented our experience up through 1948. There have been added to the fifty-three patients at the Massachusetts General Hospital reported before, another twenty-five cases, making a grand total of seventy-eight. It is in large part through our experience with this group of new patients that *modification of our previous discussion has resulted.*

Definition: Chronic constrictive pericarditis is a disease consisting primarily of obstruction to the diastolic filling of the heart because of the presence of dense, unyielding, chronically diseased pericardium.

Sometimes called by the unsatisfactory designation "Pick's disease,"† this malady has become a subject of increasing interest and importance during the past three decades. The reasons for this are two. In the first place, the condition has been one easily mistaken for something else, and, secondly, it is now possible in many cases to effect a cure by proper treatment, whereas in the past there was no adequate treatment and the disease was regarded as hopeless and necessarily carrying with it years of invalidism.

Etiology and Pathology: Chronic constrictive pericarditis always follows acute pericarditis, which may or may not itself be constrictive. Sometimes it is possible to follow the course of the case from the beginning of the acute pericarditis right through to the stage of chronic constrictive pericarditis over a period of months to years. In a good many cases, however, *it is impossible to make such an observation, the acute pericarditis* having been very insidious and frequenty undiagnosed

The majority of the patients are young (children or young adults), but the disease may appear in middle age. Both sexes are affected. In the writer's series of seventy-eight cases, fifty-nine were male and nineteen female. The ages (in years) at which the disease became manifest were as follows: to nine years, two cases, ten to nineteen, fifteen cases; twenty to twenty-nine, fifteen cases; thirty to thirty-nine, sixteen cases; forty to forty-nine, nineteen cases; and fifty to fifty-nine, eleven cases. Thus, there were only thirty of the seventy-eight cases in whom the disease became

* Also called Pick's disease, concretio cordis, and chronic compression of the heart

† Chevers in 1842 published a good description of chronic constrictive pericarditis more than fifty years before Pick (1896)

apparent after the age of forty; therefore it is preponderantly the result of infection in youth and commoner in males.

As a rule, the thickening of the pericardium consists of a fibrosis, the cause of which is usually undeterminable when the tissue is examined. Simply evidence of the result of inflammation is found, without definite indication of the cause of such inflammation. In some cases, tuberculosis is discoverable; in a few other cases, some septic infection; and in still other cases, a reaction associated with polyserositis attending a pneumonia or other infection. In most instances the etiological factor is unknown or obscure. In only very rare cases is rheumatism even a possible causative factor. In the series of seventy-eight cases observed by the writer at the Massachusetts General Hospital (proved by operation or otherwise), rheumatism has been the cause in no case. In all probability tuberculosis is the commonest cause of chronic constrictive pericarditis; it was the only clearcut factor in any cases (eight) of our series. Dr. George Pickering of England, and others also, have observed the actual evolution of chronic constrictive pericarditis in the course of years from acute and subacute tuberculous pericarditis in tuberculosis sanitaria and other such institutions.

The pericardial sac may or may not be obliterated; usually it is. It is to be recognized at the outset that obliterative pericarditis is not synonymous with chronic constrictive pericarditis, since most obliterative pericarditis does not constrict the heart, at least to any serious degree. Both layers of the pericardium may be much thickened to cause the constriction; or either layer, epicardium or parietal pericardium or both may be so firmly adherent that it is impossible to separate them or to distinguish which is the more thickened. The thickening of the pericardium may be universal or only over certain parts of the heart. In order to have the important constricting effect, however, the amount of pericardium involved is usually considerable. The posterior surface of the heart, *i. e.*, over the left ventricle and left atrium, may be more or less involved than the anterior surface, *i. e.*, over the right ventricle and right atrium. The great veins may or may not be constricted at their junction with the right atrium. There may or may not be fluid in the pericardium in addition to the thickening. When fluid is present in the pericardium, the constriction may be due more to the fluid than to the chronic thickening of the pericardium itself; such a state is not strictly to be designated chronic constrictive pericarditis, since nearly all fluid accumulations occur during acute or subacute involvement of the pericardium, and should be classed under the designation *acute* or *subacute constrictive pericarditis* (*cardiac tamponade*).

Calcification may be superimposed as a complication in chronic pericarditis. It has been present in about one-third of the writer's cases. But, again, there must be a clear differentiation between calcification of the pericardium and chronic constrictive pericarditis. There may be either without the other.

Polyserositis (sometimes called *Concato's disease*), has at times erroneously been regarded as synonymous with chronic constrictive peri-

carditis. To be sure, chronic polyserositis is frequently found with chronic constrictive pericarditis, and acute polyserositis may precede chronic constrictive pericarditis, but again, either may be present without the other.

Chronic pleuritis with adhesions is a common and relatively unimportant finding after polyserositis, but on occasion it becomes so severe that, as in the case of the pericardium, it becomes constrictive and gives rise to a condition that has been labelled by Dr. C. S. Burwell as *chronic constrictive pleuritis.*



FIGURE 1 Heart encased in constricting pericardial sac Note the fibrosed pericardium as thick as shoe leather (Courtesy of the Lancet, London)

Perihepatitis (frosted or iced liver, or Zuckergussleber), and perisplenitis, belonging to a chronic peritonitis, may be a part of a polyserositis, but they have sometimes been incorrectly attributed to chronic constrictive pericarditis itself

Finally, thick external adhesions binding the heart to the chest wall may or may not complicate chronic constrictive pericarditis. They are not part of the picture, although it is usual for the heart to be adherent to the diaphragm.

Diagnosis: No one finding is conclusive for the diagnosis of chronic constrictive pericarditis. Use must be made of the assembly of all available information, including history, physical examination, and laboratory data, particularly electrocardiography and x-ray study.

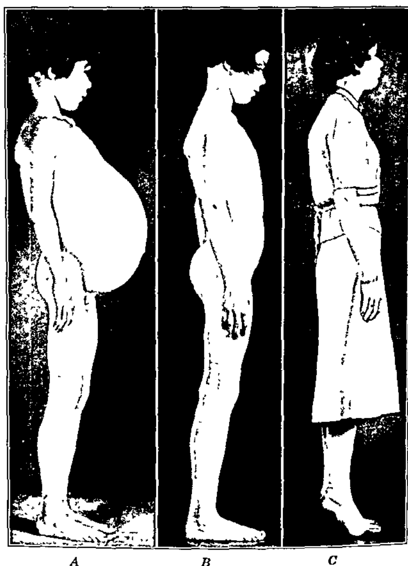


FIGURE 2. *A*, Ten years old, showing the marked ascites, engorged neck veins, and malnutrition characteristic of advanced chronic constrictive pericarditis. *B*, Same case two years later, six months after surgical cure. *C*, After another six years, still showing a normal state of the circulation.

Probably the most important diagnostic clue of all is the development, in a young or middle-aged individual, of evidence of increase in the systemic venous pressure, consisting of engorgement of the neck veins, enlargement of the liver, dependent edema, and actual increase in direct venous pressure (above 10 cm. of blood or water) in the absence of evidence of heart disease and provided acute pericarditis with effusion is not

the cause. That is, the slow onset of dropsy, particularly evidenced by enlargement of the abdomen, should cause suspicion of the diagnosis. Liver enlargement alone is not indicative of the condition, because there are many other causes for a big liver. Liver enlargement and evidence of increased systemic venous pressure are suggestive of the condition, but heart disease with failure is the common cause of such findings, and these must be ruled out at the start. The ascites that is so frequently present is in large part merely secondary to the liver engorgement.

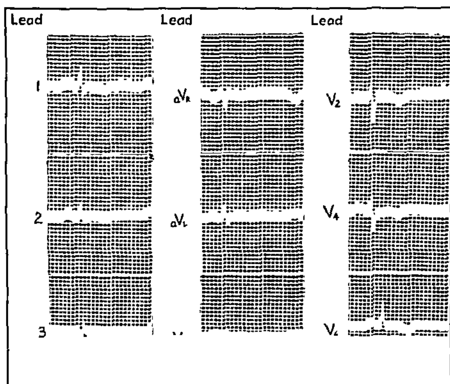


FIGURE 3 Electrocardiogram of man (S F), aged forty-one years, with chronic constrictive pericarditis Note low voltage of Q-R-S waves and abnormal T waves throughout

It is true that increase in the size of the abdomen, due to enlargement of the liver and ascites, is predominant, and often one of the earliest signs, but there are exceptions to this rule Sometimes the edema first appears in the feet, and sometimes the edema of the legs is at least as great in degree as the enlargement of the liver and ascites. This variation is probably due to the variability of the relative increase in pressure in the hepatic veins and in the inferior vena cava. There is also sometimes slight edema of face, chest wall, or arms, especially after recumbency.

It is of great importance and help in the diagnosis to have had a clear history of acute pericarditis with friction rub or effusion preceding the signs and symptoms of chronic constrictive pericarditis by months or years.

Other signs that are helpful in establishing the diagnosis are a small arterial pulse pressure with a tendency to the so-called paradoxical pulse (a sharp decrease in systolic and pulse pressure during inspiration) and the tendency for the heart to remain fixed in its position during respiration and change in position of the body. It is possible, however, to have the heart chronically constricted by a thickened pericardium while it remains completely or almost completely mobile, due to the fact that there are no important external adhesions. Broadbent's sign is generally absent.

The size of the heart may be normal or slightly to moderately increased; it is never markedly increased when an uncomplicated case is dealt with, and most of the cases are uncomplicated. There are no important murmurs, although systolic murmurs at the apex are not rare. There is frequently a loud third sound in early diastole, heard best at the left of the sternum; it is not diagnostic. Normal rhythm is the rule; in some cases, however, there is atrial fibrillation. It was present in twenty-two (twenty-eight per cent) of the author's seventy-eight cases. And in a few cases (four) there was atrial flutter. In very infrequent cases there may be independently, heart disease and chronic constrictive pericarditis. The writer has encountered two such cases, one with congenital heart disease, and one with rheumatic heart disease.

The *symptoms* are relatively unimportant. There may or may not be dyspnea. There may or may not be weakness. There may or may not be malnutrition (in the severe cases this is practically always present). There usually is no pain. The patients tend to be semi-invalids.

Laboratory data are of considerable help, especially *electrocardiograms.* Almost invariably the electrocardiogram shows either low voltage of the QRS waves in the classical limb leads, or abnormality of the T waves (flattening or inversion), or both. The electrocardiograms in some of the cases resemble those of coronary heart disease, but the changes are less characteristic and more diffuse or extensive. Right axis deviation, usually with atrial fibrillation and hence resembling the pattern of marked mitral stenosis, may be found in a few cases with relatively greater constriction of the left than of the right heart chambers.

X-ray evidence is generally helpful, but there are occasional cases in which little or no abnormality can be found, the heart moving quite freely and even with fair pulsation of the left border. Calcium, when found, is an additional help in confirming the diagnosis when other signs are present. Often the heart and mediastinum are fixed or displaced a bit to one side or the other, or there is an increase in thickness of the mediastinum. Also, frequently there is an obscurity of the borders of the heart, and occasionally little or no pulsation is visible anywhere along the heart borders. Observation of the pleura is important because if the pleura is very much thickened, there is evidence suggesting chronic polyserositis as a background for the chronic constrictive pericarditis Chronic constrictive pleuritis may accompany chronic constrictive pericarditis

Some of the increase in heart size indicated by x-rays is to be accounted for by the actual increase in thickness of the pericardium, which may reach ½ to 1 cm. on either side of the heart. In occasional cases the

lung hilus shadows are increased and there is more indication than usual of involvement of the left ventricle and left atrium by the chronic constrictive pericarditis, as noted particularly by calcification. In such cases there may be evidence of enlargement of the right ventricle due to the strain on that heart chamber from pulmonary hypertension secondary to constriction of the left heart chambers, somewhat comparable in mecha-

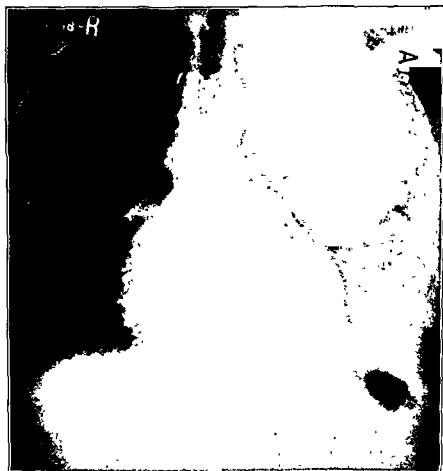


FIGURE 4 X-ray picture (teleroentgenogram) of heart and pericardium of case of chronic constrictive pericarditis with calcification Note the shell of calcium just outside the shadow of the left heart border and along the diaphragmatic border

nism to the effect of mitral stenosis; it is such cases that are more likely to show atrial fibrillation.

It is of considerable importance in the future study of cases of chronic constrictive pericarditis to determine the pulmonary arterial blood pressure by cardiac catheterization, since the direction of the surgical approach and the success of the operative therapy may depend on this finding. If the pressure is higher than normal, there should be a wide anterior (*e. g.*, sternum splitting) or lateral approach to free the left as well as the right

heart chambers from their preponderant constriction. It is probably wise to make such an approach in all cases in the future.

Other laboratory information is of little help. The blood counts may be normal or show some degree of anemia. If there is leukocytosis, a subacute pericardial or polyserositic infection or some other complication must be suspected. The serum protein may or may not be reduced; it is reduced in severe cases with malnutrition. Liver functional tests may or may not show slight reduction, but there is no evidence in uncomplicated cases of severe liver damage, although some degree of "cardiac cirrhosis" of the liver is not uncommon. There is never any jaundice (unless there is a complicating pulmonary infarction) or bile in the urine. Special studies have shown a decreased output of the heart in accord with the other findings. The reduction may be to less than fifty per cent of the normal, with inability to show an appreciable increase on exercise, the pulse rate tending to be unusually elevated in these patients as the result of the heart's effort to produce a satisfactory circulation. The systemic venous pressure is always elevated, sometimes up to 300 mm. or more. The circulatory rates are also delayed.

Differential Diagnosis: In the differential diagnosis there are three conditions which are particularly likely to be confused with chronic constrictive pericarditis. The first of these is *mitral stenosis with congestive heart failure.* The differential diagnosis should be easy in nearly every case of this sort. The presence of a mitral diastolic murmur at the apex is practically pathognomonic of mitral stenosis and has not been encountered in any of the writer's cases of chronic constrictive pericarditis It is important to listen at the apex, however, for this murmur, since it may be localized, and it was the failure actually to listen at the apex itself which was responsible for the erroneous diagnosis of constrictive pericarditis in two cases referred to the writer. In these patients the apex had become situated in the anterior axillary line with increasing enlargement of the heart. In most cases with congestive failure the heart is considerably enlarged, a finding not consistent with chronic constrictive pericarditis. Also, there are more likely to be atrial fibrillation and right axis deviation with mitral stenosis than with chronic constrictive pericarditis, although several of our cases (twenty-two out of seventy-eight in number) observed have shown atrial fibrillation, a few (four in number) have had atrial flutter, and several have shown some right axis deviation, due quite likely to the greater pericardial constriction of the left than of the right heart chambers.

Cirrhosis of the liver is a second condition to be differentiated from chronic constrictive pericarditis. This is easily done by the finding of increased systemic venous pressure in the latter condition. The neck veins are always engorged in chronic constrictive pericarditis, while in hepatic cirrhosis they are prominent only when there is an excessive amount of ascites displacing the heart and great vessels upwards. Slight degrees of "cardiac cirrhosis" of the liver may, however, be induced by chronic constrictive pericarditis.

Polyserositis is the third condition that is sometimes confused with

chronic constrictive pericarditis. The presence of an acute infection with fluid in the pleural cavities and pericardium, and sometimes in the peritoneal cavity, is not "Pick's disease," although it may precede it. One of the difficulties here, however, is that in complicating chronic constrictive pericarditis itself there may be a good deal of pleural effusion, sometimes extensive, especially in the severer cases. The effusion is in the nature of a transudate, as a rule, although the differentiation between transudate and exudate is often difficult. The evidence of signs of persistent infection is the most important clue in such cases, along with the examination of the fluid obtained from the various body cavities.

Nutritional edema is easily distinguished from chronic constrictive pericarditis because of its diffuseness and the usual absence of liver enlargement and ascites, along with the history of the causative factor of malnutrition and the very low serum protein.

Tricuspid valve disease of high degree is so rare that it hardly needs to be mentioned, but it must be considered in some of the cases. Since it nearly always complicates mitral stenosis, it is usually easily ruled out. It is, however, comparable to chronic constrictive pericarditis in one particular, namely, its tendency to cause *long-continued* invalidism or semi-invalidism, lasting for years, with recurrent ascites that may need repeated paracentesis. Tricuspid stenosis complicating mitral stenosis adds to the duration of life that would be expected in systemic venous congestion due to mitral stenosis alone.

Course and Prognosis: Most patients with chronic constrictive pericarditis live for years. Their longevity and activity vary, however, very greatly, depending on the amount of the cardiac constriction, on complications, and on the degree of success of surgical treatment There tends to be a state of prolonged semi-invalidism with occasional or frequent abdominal paracentesis unless surgery affords a functional cure In the writer's own series of seventy-eight cases studied during the past twenty-seven years (1928 to 1955, inclusive) there has been a wide range of experience, from one case who had progressed so rapidly downhill in the course of six months that she was too serious a risk for surgery and died of the disease shortly after entering the hospital, and another case who, severely affected, died at the end of the operation, to a mild case who was still alive and at work (as a physician) forty years after his acute pericarditis and onset of evidence of the disease, not requiring operation, and a young woman, now perfectly well twenty-seven years after pericardial resection done when she was practically a complete invalid. Thirty-two of the sixty-three patients operated upon in the writer's series have been cured functionally by surgery in the last twenty-seven years and most of these are well and active today. All six of our patients who have been followed for over twenty years are living normal unrestricted lives. Ten other patients have been followed for over ten years and eleven for over five years.

Treatment: The only satisfactory treatment for chronic constrictive pericarditis is surgery. Digitalis is of no avail except in cases of atrial fibrillation where it controls the heart rate at a level which is optimal for

the most favorable circulation in a given case. Diuretics, either by mouth or intravenously, are only temporarily helpful. They may, however, aid in tiding a patient along for months or years if his condition is for any reason inoperable, or if the patient refuses surgical treatment. They are helpful also in preparing the patient for operation. The best diuretic for the purpose is either mercuhydrin, 1 to 2 cc., intramuscularly, or thiomerin, 1 to 2 cc., subcutaneously, at intervals of one to four weeks, as needed, with or without the aid of ammonium chloride (1 Gm. [15 grains] three times a day) or other diuretic by mouth. Paracentesis is invaluable in the cases not operated upon and in preparing the patients for operation. Usually such paracentesis is confined to the abdomen, but now and then the chest cavities need to be emptied also. In the old days these patients were subjected to abdominal paracentesis once every week or two or three for years on end, a very disagreeable but necessary act.

Finally, before proceeding to the radical cure of chronic constrictive pericarditis, two palliative measures of value may be mentioned, *i. e.*, limitation of physical activity, and restriction of fluid, food, and salt intake.

Exercise, by increasing the demand of the body for an active circulation, almost invariably aggravates the condition and the degree of congestion A patient with chronic constrictive pericarditis who attempts to carry on his normal life is almost sure to grow worse despite other medical measures. He adds weight in the form of fluid in the abdomen and extremities. When he rests completely in bed, he usually improves rapidly for a while, and has a spontaneous diuresis. At half or mild activity he is able to carry on, sometimes fairly well if not badly affected. Some patients, however, are so seriously damaged that they must remain complete invalids and even then may go on to early death. The individual patient quickly finds his optimal level of activity.

From the beginning it was appreciated that the more salt and fluid ingested by a patient with chronic constrictive pericarditis, the more pronounced were the signs and symptoms of congestion. Of particular importance is a restriction of total sodium intake; a reduction to 1 or 2 Gm. of sodium chloride instead of the usual 10 to 12 Gm. per day may suffice. Very interesting experiments with respect to fluid and salt intake were made on himself by Finsen and reported in 1894 and 1904.

Surgical Treatment: Most patients are reasonably good subjects for efforts at surgical cure. Thoracic and especially pericardial surgery has been so much developed in recent years that operation can be approached by a skilled, trained surgeon nowadays with little hesitation. Much care, experience, and judgment, however, are needed for a high percentage of success. A suitable case for surgery may be considered to be an individual who can be made largely free of congestion by medical measures and who seems otherwise in fairly good condition, but who is incapacitated by the disease itself. There are a few individuals who are so sick that operation is contraindicated, and death may come when an attempt is made to operate on such patients. They are those with very extensive constriction, not much relieved by medical measures and paracentesis.

It is of great importance, furthermore, to recognize that the disease may progress to a relatively early fatal termination. The speed of the increase of the constriction varies very greatly in different individuals. In some cases, a few weeks or a few months may mean the difference between life and death.

Technic: The surgical operation itself may be carried out either anteriorly or laterally. In the former case it consists first in resecting the ribs overlying the heart, usually with removal of several inches of the fourth, fifth and sixth ribs, and costal cartilages on the left side, along with resection by special blade of the left part of the sternum. It is of considerable importance to identify and retract the pleurae, which are also often thickened and out of their normal positions. When anesthesia was carried out, as used to be the practice at the Massachusetts General Hospital, under tracheal insufflation of ether and oxygen, with the patient in the sitting position in a dental chair, there was found to be no great harm in allowing air to enter the pleural cavities if by chance they should be opened.

During recent years, however, we have had interesting and important experiences with the relief of several patients by either the left lateral or the sternum-splitting surgical approach so that the surgeon can decorticate the posterior as well as the anterior heart chambers. The very first case in which the lateral approach was carried out (Case 2, to follow) is well today nearly nine years after his third operation, the first two operations with anterior decortication having been unsuccessful.

The pericardium is identified and opened near the apex of the heart. If it is completely adherent, it has to be incised and an attempt made to peel it off from the heart itself The actual process of decortication of the heart, sufficient at least to give some relief, usually takes about one hour. Since the involvement is usually extensive both anteriorly and posteriorly, the decortication begins near the apex and extends up over both ventricles and atria, and, if necessary, down over the inferior vena cava and up over the superior vena cava, although usually there is not much involvement of the veins. (In one case observed, a calcified band was excised from its position overlying the inferior vena cava)

The pericardium should not be cut off in large masses. There should always be a small bit of pericardium left attached to the heart in case of rupture of the wall of either ventricle or atrium; if the wall is torn, the pericardial tab may be sewed over the rupture. This was done in two of our successful cases.

How much of the posterior heart chambers, *i. e.*, the left ventricle and left atrium, should be decorticated is for the surgeon to decide. Some of the writer's cases have given evidence of extensive posterior constriction, but decortication of the posterior heart chambers was not attempted in the early days by us although a case had been reported in Germany in whom there was a successful decortication, first of the anterior surface of the heart, and, at a later operation, of the posterior surface of the heart.

During the operation it is encouraging to find the heart increasing visibly in size and degree of pulsation while it is being decorticated. The

pulse pressure may definitely increase during the operation. In one of our patients the pulse pressure increased at once from twenty to forty, with obvious improvement in the heart's action. Good judgment must be used in deciding when to stop the operation. It is to be recognized that it is possible to carry out a second operation if the first has not been complete enough. This has been done in eleven of the writer's cases, and the approach the second time proved as a rule to be very easy, there being no ribs to remove and no pericardium to penetrate first in approaching the field of operation. The reformed adhesions were nonconstricting.

The patient is returned to the ward and kept in an oxygen tent for the first day or two, or as long as may be needed. Great care postoperatively to empty the pleural cavities of fluid, if they fill rapidly, and expert nursing are essential. Some patients recover very quickly with spontaneous diuresis directly after the operation, while others take months for their improvement, the cure going on progressively for close to a year. Still others show little or no improvement, and a few cases may die as a result of the operation.

In our series of seventy-eight cases of this disease at the Massachusetts General Hospital, sixty-three patients were operated upon (fifty-two, once; seven, twice; four, three times). Of these sixty-three patients, thirty-two were cured so far as chronic constrictive pericarditis is concerned; and twenty-two have died, four on the operating table because of the severity of the illness, one the day following operation, two two days after operation, one six days after the operation, and twelve others months later from the disease itself or from complications. Unexpected accidents may sometimes occur in cases that otherwise seem favorable. Such happened during operation in two of our very young patients; in one of these the atrium was torn during the pericardial resection, but the tear was quickly repaired by the use of a bit of the pericardial flap still attached, and no harm was done, for she is well today over twenty-two years later; in the other patient (a girl of thirteen) at the end of the operation the right heart, which was very thin, dilated to a high degree, and death came in a few minutes, apparently as a result of the failure of the right side of the heart.

In the patients that have been cured clinically, there has been a disappearance of all evidences of congestion, except that there may still be a slight elevation of the venous pressure above the normal, and persistence of slight enlargement of the liver. The electrocardiogram may remain abnormal, but frequently it improves in appearance.

ILLUSTRATIVE CASES

Chronic constrictive pericarditis varies so greatly in its manifestations and response to treatment that it will be helpful to present certain illustrative cases. The first will show the excellent curative result in a severely affected young child. The second will illustrate the important advance in surgical approach and technic.

CASE 1: *Successful result of operation in a severely crippled child:*

B. K., now (August, 1955) aged thirty-three years This girl was reported in

full up to 1935 in the Lancet, London, September 7 and 14, 1935, pages 539 and 597, as follows:

"B K., a girl aged ten, entered the hospital on October 13, 1931, with a history of having lived a semi-invalid life since the age of 5½ due to a markedly enlarged abdomen resulting from the presence of much ascitic fluid When she was twenty months old she suffered from what was apparently an attack of acute pericarditis, and her abdomen became enlarged. At the age of 2½ years a laparotomy was performed and a gangrenous appendix was removed No tubercles were seen on the peritoneum at the time of operation A drain was inserted, and the patient made a good recovery. The fluid returned in about three weeks, but following an abdominal tap one month later there was no recurrence of fluid for three years. At the age of 5½ the abdominal fluid returned, and six months later a Talma operation (omentopexy) was done Abdominal fluid injected into a guinea pig gave negative results There was no improvement following this operation, and at the age of nine the patient entered a second hospital for further study. Her abdomen was tapped at that time, but not again after that until her entrance into the Massachusetts General Hospital in the fall of 1931 when 6240 cc of straw-colored fluid with a specific gravity of 1 013 were removed

"Her mother had died of tuberculosis during the patient's infancy Her father is living and well

"Physical examination showed a thin, somewhat pale, young girl with heart apparently normal in size and sounds and without murmurs, and with prominent jugular veins and a large protuberant, nontender abdomen, filled with fluid (Fig. 2*A*). X-ray examination showed heart and great vessels somewhat displaced to the right and anchored to the diaphragm; no pulsation was evident at the right border of the heart and great vessel shadow, the right pleura was thickened.

"The electrocardiogram showed normal rhythm, rate 100, with inverted T waves in Lead II.

"Advice was given at that time that the chest be explored surgically and the adhesions constricting the right auricle, right ventricle, and the great veins be freed.

"After an interval of two years this girl returned to the hospital in an unchanged condition with persistence of the enlargement of the abdomen. The serum protein measured 4 3 per cent. X-ray and electrocardiographic findings were as before

"Pericardial resection was carried out on November 16, 1933, and a moderately thickened pericardium containing calcareous plaques was removed from over the right ventricle and right auricle by Dr Churchill The pericardial tissue that was removed showed fibrosis and calcification on examination There was a stormy time for two days after the operation, and during the first two weeks there was no apparent improvement About four weeks after the operation spontaneous diuresis began, and in the course of a few months the ascites completely disappeared (Fig 2*B*). She has been in excellent health since, and was well when she was last heard from.

"The electrocardiogram on May 16, 1935, showed normal rhythm at a heart rate of 80, with slightly upright T waves in Lead I, flat T waves in Lead II, and very slightly inverted T waves in Lead III; this record differed from that taken before the operation in that the T waves were more normal and the voltage of the QRS waves was greater."

Follow-up in July, 1939: "Good health and rapid growth have characterized the last four years except that during the past few months there has been some

evidence of easy fatigability. Physical examination now shows a tall, slender, somewhat delicate appearing girl (Fig. 2*C*) with normal heart sounds and size The electrocardiogram shows normal rhythm, rate 95, slight right axis deviation, low T waves in Lead I, inverted T waves in Lead II, and inverted T waves in Lead III.

"Blood examination shows a normal smear, minimal achromia, and no abnormal cells.

"The rapid growth and slight anemia in this girl are responsible for her present somewhat frail state of health, but fundamentally she seems all right and there is no evidence whatsoever of any recurrence of the trouble associated with her constrictive pericarditis for which the operation was so successfully carried out six years ago. See the illustration herewith showing her in 1931, 1933, and 1939 (Fig. 2)."

"*September, 1948.* Her father reports excellent health in every respect."

May, 1955. Examined by us and found to be in perfect health.

CASE 2: R. P., male, aged twenty-one, was admitted to the Massachusetts General Hospital in September, 1944, with a diagnosis of chronic constrictive pericarditis already recorded. The discovery of pericardial calcification had been made in March, 1943, by x-ray examination of the chest incident to routine check-up for his fitness for military service. He had no symptoms at that time On admission to the hospital in September, 1944, he showed good development and nutrition with a regular pulse rate of 80 The blood pressure was 120/80 The heart seemed of normal size, the pulmonary second sound was louder than the aortic second, and there were no murmurs. There was no enlargement of liver or spleen There was no evidence of peripheral edema. Venous pressure was at the normal upper limit with a "Burwell end-point" of 117 mm of water The total serum protein was 7.4 Gm. Blood and urine examinations showed no abnormalities. Electrocardiogram showed inversion of the T waves in all leads X-ray examination confirmed the presence of calcification of the pericardium, evidence of old pleurisy at the left base, and a small amount of fluid in the right pleural cavity.

On October 6, 1944, Dr Richard Sweet performed cardiac decortication using the anterior approach. The entire frontal portion of the pericardium, including a calcified band 38 mm. (1½ inches) in width over the atrioventricular groove, was removed The postoperative course was uneventful and he was discharged at the end of the month

During the next year and a half this young man remained in fairly good health, doing light secretarial work with no difficulty. In the spring of 1946 he had begun to notice progressive increase in the size of his abdomen, shortness of breath, and increase in weight. Also there had been noted at about the same time the onset of atrial fibrillation. Therefore, on June 5th, 1946, he was readmitted to the Massachusetts General Hospital. On this occasion his venous pressure was much increased, to 265 mm. of water. The heart was enlarged with pulmonary second sound of greater intensity. The liver was slightly enlarged and tender. There was occasional edema of the ankles. His blood pressure was 108/84. The heart rhythm was grossly irregular at a rate of 82. The electrocardiogram confirmed the presence of atrial fibrillation and showed the same abnormalities as before in the T waves The total serum protein measured 7 Gm per cent.

On June 20th, 1946, a second pericardial resection was carried out by Dr. Sweet. The site of the original incision was used again More calcified pericardium was removed, particularly over the area of the right atrioventricular groove. At first, postoperatively, he seemed definitely better but within a month

of his return home his original symptoms recurred despite treatment with low sodium intake, digitalis, ammonium chloride, and intravenous mercupurin.

On December 10th, 1946, having become obviously much worse in the interval of several months, he returned to the Massachusetts General Hospital. At this time the neck veins were very prominent and pulsating with a venous pressure of 300 mm of water A paradoxical pulse was present. The rhythm was regular at a rate of 82 The blood pressure was 108/76. The liver was felt 7½ cm. below the costal margin. There was slight to moderate edema of the ankles The electrocardiogram now showed, in addition to atrial fibrillation, definite right axis deviation which had been developing in the interval of the two years since the first operation.

Because of the failure of the previous operations, the right axis deviation with atrial fibrillation which resembled the pattern of mitral stenosis, and the accentuation of the pulmonary second sound, it was now believed that he had constriction of the left heart chambers However, to make sure of this, cardiac catheterization was carried out in order to measure the pulmonary blood pressure This was kindly done for us by Dr Lewis Dexter at the Peter Bent Brigham Hospital who found that the pulmonary arterial pressure was 72 mm. mercury; that is, three times the normal

Therefore, on January 17th, 1947, after careful preoperative preparation a third pericardial resection was carried out by Dr. Sweet, using the left lateral transthoracic approach The operative note was as follows

"A long oblique incision was made starting in front close to the previous pericardiolysis incision, extending laterally under the breast and up beneath the pectoral fold as far as the midaxillary line. This incision was enlarged through the sixth interspace and on inserting a rib-spreader, after freeing the adhesions of the lung, an excellent exposure was obtained. The lung was densely adherent to the parietal pleura both beneath the ribs and along the mediastinal surface. The mediastinal adhesions were separated and the lung was retracted posteriorly and laterally. This gave an excellent exposure to the left posterior aspect of the pericardium. The phrenic nerve was identified and held aside with a retractor The previously denuded section of heart appeared to be functioning well This included the right ventricle and a very small portion of the left The apex had been freed previously, but there had been considerable re-formation of constricting fibrous tissue in this region This was freed and the remainder of the pericardium, which enveloped and held in a constricting vise the left ventricle, was released with moderate difficulty It was adherent almost everywhere with very dense adhesions, in some of which were actually plaques of very thick calcium requiring cutting with heavy scissors, but it was possible by freeing them to release the left ventricle completely all the way around behind. The *pericardium in this region was removed from the diaphragm and as far around* in back as the inferior pulmonary vein. Superiorly it was freed over the atrioventricular groove and the appendix of the left atrium which was held down in a vise of calcium was finally freed and was seen to retract upwards. A rather large segment of pericardium was removed from the atrial portion as well as from the ventricular portion It was felt at the completion of the operation that a very wide liberation of the left ventricle and left atrioventricular septal groove had been accomplished The patient stood the operation well and the color of his blood was normal at its completion although in the beginning he was very cyanotic until the heart had been freed The lung expanded well A catheter was left in the space between the heart and the lung in order to provide for evacuation of serum and possibly any air which might result from an undiscovered leak from

the lung itself. This was brought out through the center of the incision to be removed in twenty-four hours. The wound was closed in layers by means of interrupted silk sutures with several pericostal sutures of catgut in the intercostal portion of the incision"

After a stormy postoperative course for two weeks he began to improve and when discharged from the hospital at the end of February, 1947, the venous pressure had dropped to 190 mm. of water and he showed a definite decrease in congestion.

Later examinations have shown progressive improvement When seen in December, 1947, he felt quite well, requiring no treatment except for the maintenance of digitalis He was free from congestion The venous pressure had dropped to 167 mm of water. He has remained perfectly well since then (note made in November, 1953).

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CLAUDE S. BECK, M.D.

22

Surgery of the Heart and Pericardium

Introduction: The application of the aseptic principle which was introduced some seventy years ago marks the beginning of modern surgery. Sepsis and secondary hemorrhage were banished by the aseptic methods and the dread of operation began to disappear after these methods were introduced. A great development in surgery took place in a relatively short period of time. All parts of the body were explored. The chest presented special problems which delayed the development of thoracic surgery. Who of the surgical pioneers living in the early aseptic period desired to remove a lung when the appendix, uterus, gallbladder, breast, kidney, thyroid, etc., were more accessible! Who, also, desired to operate upon the heart—an organ that is always in motion—possessing a great capacity for hemorrhage, and possessing also a constant threat of stopping! It is not surprising then to find a comment of this nature from Billroth, the pioneer in gastric surgery, made in 1883, as follows: "The surgeon who would attempt to suture a wound of the heart would lose the respect of his colleagues." Wounds of the heart were considered to be necessarily fatal. This was the general belief for many centuries.[1] The first experiments on cardiac wounds that I can find in the literature were carried out by Block on rabbits in 1882. He produced stab wounds of the heart, successfully sutured the wound and advocated suture of the wound when the human heart was stabbed. In 1895 Del Vecchio demonstrated the healed scar that followed a wound that he had made in a dog's heart. His demonstration was made before the Eleventh International Medical Congress at Rome and it attracted attention. Shortly thereafter, September 4, 1895, the first operation on the human heart was performed by Alex Cappelen of Christiania. Thus the heart entered the domain of surgery.

Cappelen's Case: A man, aged twenty-four, received a stab wound in the fourth left interspace in the midaxillary line He walked home bleeding from [illegible]

so that the pulse could be felt, and consciousness returned There was dulness to percussion over the left side of the chest.

At operation chloroform anesthesia was used. The third and fourth ribs on the left side were resected The intercostal artery was not cut The left pleural



FIGURE 1 Alex Cappelen (1858-1919) performed the first operation upon the human heart

cavity contained 1400 cc. of blood The lung was not injured. Bleeding continued from the depth of the operative field and an opening in the pericardium large enough to admit the tip of the finger was found The pericardium was distended with blood It was opened. A wound in the left ventricle 2 cm long was sutured with chromic catgut and a bleeding coronary artery was ligated The rhythm of the heart was regular throughout the operation.

During the postoperative period, which lasted two and one-half days, the pulse was rapid; cyanosis was present, and there was a slight fever. The cause of death was anemia and pericarditis The wound had not penetrated into the cavity of the left ventricle The bleeding had occurred from the coronary artery.

Classification of Heart Disease: These may be divided into the congenital and acquired forms. The congenital group includes a wide variety of conditions such as septal defects, valvular and subvalvular stenoses, malpositions of blood vessels, and a variety of shunts. The acquired group includes stenosis and occlusion of coronary arteries, valvular defects, blood clots within the heart, tumors of the heart, aneurysms of the heart, and other rare conditions. Another classification of diseases is based upon the location of the disorder whether it be extrinsic and outside the heart or extrinsic and inside the heart.

ADHESIONS TO THE HEART[2]

This is one form of extrinsic lesion It was formerly taught that adhesions produced cardiac hypertrophy and failure and the Brauer operation of cardiolysis was evolved to treat this condition. This operation consisted of removing the precordial ribs and cartilages so that the heart pulled upon soft yielding structures rather than the unyielding ribs This operation and the rationale upon which it was based have been given up. However, Hosler and Williams have shown that adhesions can disturb heart action by *rotating the heart in either a clockwise or counterclockwise direction* and by angulation of the heart from its normal position. These disturbances in position produce tachycardia but they are rarely seen clinically except at the operating table. At operation these disturbances are not tolerated except for short periods of time. Compression of the heart is another form of extrinsic lesion. This condition is produced by tight scars upon the heart or by fluid or tumors around the heart.

COMPRESSION OF THE HEART

Physiology:[3] Under normal conditions the pressure upon the heart and the great vessels at the base of the heart is negative or less than the pressure of the atmosphere. This negative pressure is produced by the elastic recoil of the lungs and measures 4 to 6 cm. of water. Likewise, the pressure within the venae cavae is negative by several centimeters of water. The walls of the cavae are soft and collapsible and readily yield to pressures from within or from without. Let us consider the effect of an increased pressure in the pericardial cavity such as occurs when the heart is stabbed and bleeding takes place from the wound. As the heart and intrapericardial segments of the venae cavae are compressed by the accumulated blood we find that the venae cavae and the right auricle become collapsed. *The flow through these structures is immediately reduced and*

the blood is held back in the venous system. The venous pressure immediately begins to rise and if it can rise sufficiently high to overcome the collapsing effect of the intrapericardial blood, filling of the heart is resumed. If additional bleeding occurs so that the intrapericardial pressure is again increased we find that a repetition of events takes place, namely, slowing or stopping of the blood stream in the cavae and elevation of

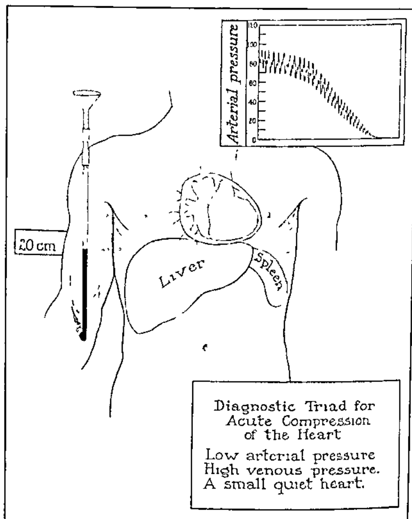


FIGURE 2. Triad for acute compression of the heart.

venous pressure. It is apparent that a definite relationship exists between the pressure outside and the pressure inside the venae cavae. There are certain limits above which the pressure outside the cavae cannot rise and these limits are determined by the heights to which the venous pressure can rise. In acute conditions the venous pressure can rise to 15 or 20 cm. of water. In chronic conditions the venous pressure can rise to 42 cm. of water. Acute and chronic pressures above these respective levels can be considered as fatal.

The amount of pressure that the heart and venae cavae can tolerate

depends upon several factors. One of the factors that determines the amount of pressure that can be tolerated is the rapidity with which the pressure is built up in the pericardial cavity. If it develops slowly it can go up to levels that are definitely higher than if it develops rapidly. These higher chronic pressures are made possible because in the chronic conditions the venous pressure rises to higher levels than it does in patients with acute compression.

Two factors help to elevate venous pressure in the chronic diseases. One is an increase in the circulating blood volume. The other is an increase in venous pressure produced by the waterlogging of the body. An interesting observation that we made relative to venous pressure, in patients with chronic compression, was that the venous pressure fell when large quantities of fluid were removed from the abdomen. This was due to the relaxation and engorgement of venous channels in the abdomen after the abdominal tension was released. An abdominal binder restored venous pressure to its higher levels. Other points of therapeutic value along this line can be mentioned.

It is well to remember that venous pressure can be raised by the addition of fluid intravenously and that pressure upon the heart can be reduced by the aspiration of fluid from the pericardial cavity. In those cases demanding urgent treatment these procedures are of value while preparations for operation are being made. It should be noted that an elevated venous pressure is essential in cases of compression. However, after the compression agent has been removed the high venous pressure becomes something of a danger in that it dilates the heart.

In one of my patients the heart failed after a compression scar had been successfully removed. The heart dilated and failed. In certain cases showing very high venous pressures, bloodletting is sometimes indicated after the compression lesions are removed by operation. This will reduce venous pressure and will lessen the degree of dilatation of the heart.

The compressed heart is always a small heart. It cannot dilate. It cannot undergo hypertrophy. It is an efficient organ and does not waste energy. It receives a subnormal quota of blood and it pumps out a subnormal quota of blood. In pumping out a subnormal quota of blood it performs a subnormal quota of work. The heart can do nothing about the reduction in work-load. It plays a passive role and receives whatever blood the venae cavae can deliver to the cardiac chambers. Inasmuch as the work-load of the heart is reduced, the heart muscle undergoes atrophy. The heart muscle undergoes disuse atrophy in exactly the same way as any other muscle in the body undergoes atrophy when it is not allowed to perform its full normal function. Roberts and Beck showed that the measurements of the heart muscle fibers in the compressed heart were smaller than normal. The entire muscle-mass of the compressed heart is less than that of the normal heart.

Acute Compression Triad:[4] Acute compression of the heart is produced always by a fluid agent, such as blood, pus, gas, transudate, or any combination of these. The fluid is either in the pericardial cavity or in the mediastinum. Stab wounds of the heart or great vessels are a common

cause of compression. It occurs also in purulent pericarditis and it can occur as a complication following an operation in the mediastinum.

A triad of signs has been formulated by the writer for the diagnosis of acute cardiac compression. The triad consists of a small quiet heart, a falling arterial pressure and a rising venous pressure (Fig. 2). All other mani-

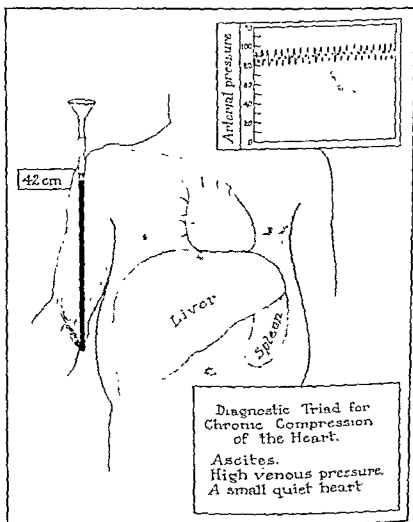


FIGURE 3. Triad for chronic compression of the heart.

festations are secondary to these. Such secondary manifestations are distant heart sounds, absence of precordial pulsation, dyspnea, excitement followed by unconsciousness, cold clammy skin, and fever in the presence of infection.

The treatment depends upon the lesion producing compression. In the traumatic cases the blood clot should be removed and the injured structure repaired. In the infected lesions the pus should be evacuated. Penicillin should be given.

Chronic Compression Triad:[1] Chronic compression of the heart can be produced by a variety of lesions. Compression by the formation of scar

tissue around the heart and in the parietal pericardium is the commonest cause. Blood, pus, transudate or exudate in the mediastinum or pericardial cavity can produce chronic compression. Neoplasms, localized abscess, bands of scar tissue over the auricle or venae cavae can produce the compression syndrome. Adhesions to the heart never produce chronic compression.

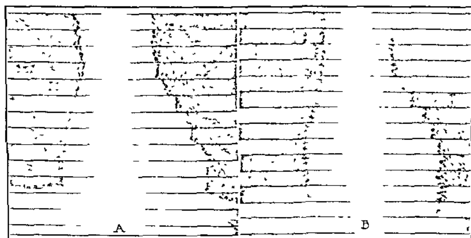


FIGURE 4 Reproduction of kymograph roentgenogram in patient with generalized cardiac compression due to scar The serrated outline indicates the amplitude of pulsation The roentgenograms are taken with a lead grid containing transverse slots in front of the plate The plate moves during the exposure so that every phase of systole and diastole is recorded on the plate *A*, Before operation *B*, After operation Note the increase in amplitude of pulsation after operation

A triad of signs has been formulated by the writer for the diagnosis of chronic cardiac compression. This triad consists of a small quiet heart, a high venous pressure as measured in a vein of the arm, and ascites together with a large liver (Fig. 3). This diagnostic triad cannot be wrong There should never be any confusion or mistake in making this diagnosis. No special tests are necessary. Indeed the diagnosis can be made by simple observation of the patient. The presence of cyanosis of the hands, lips, ears, and face, and the prominent veins in the neck and arms point to stasis in the superior vena cava. The next observation is of the abdomen. Ascites points to stasis in the inferior vena cava. The precordium is next observed and if there is no visible pulsation present the patient has chronic compression—not constrictive pericarditis, not adhesive pericarditis, not Pick's disease, not Concato's disease, not mediastinopericarditis These terms are confusing While the diagnosis of chronic cardiac compression can be made by simple observation alone, it does not tell the nature of the anatomical lesion producing the compression. The lesion must be determined by additional data. A very large pericardial shadow in the x-ray indicates fluid in the pericardial cavity and the fluid can be blood, pus, transudate or exudate. A smaller shadow indicates a compression scar and an asymmetrical shadow indicates a neoplasm, a dermoid cyst or a localized abscess.

The secondary manifestations of chronic cardiac compression consist of subcutaneous edema which may not be marked, hydrothorax of variable amount, a venous pressure measuring 18 to 42 cm. of water, dilated veins, cyanosis, elevated cerebrospinal fluid pressure, decreased circulation time, increase in circulating blood volume, distant heart sounds without murmurs, pulsus paradoxus, auricular fibrillation, auricular flutter or a normal mechanism, reduction in amplitude of the heartbeat, pulse pressure of about 20 mm. of mercury, reduction in cardiac output to as little as 22 cc. per beat in an adult, slurring and low voltage of the electrocardiogram, weakness and malnutrition. Fixation of the heart and fixation of the electrical axis are not important for diagnosis. Reduction in amplitude of the heartbeat can be shown by the kymograph roentgenogram (Fig. 4)

TRAUMA

Penetrating Wounds of the Heart

These are stab wounds and bullet wounds. Any of the component structures of the heart can be injured—auricular or ventricular wall, interventricular septum, coronary arteries and veins, the conduction system, any of the valves, the great vessels at the base of the heart, and the parietal pericardium. A foreign body can enter the heart through the skin, through the esophagus or through the venae cavae or pulmonary veins. Infection can be carried in from the outside. A thrombus can form in one of the cardiac chambers at the site of the wound. The thrombus can be swept into the lung or into the peripheral circulation. Hemorrhage can occur from the heart or from the great vessels. If the blood escapes from the pericardial cavity into the chest or into the mediastinum or to the outside, exsanguination can occur. Compression of the heart is produced if the blood does not escape and remains locked in the pericardial cavity.

The functional disturbances produced by cardiac trauma are dependent upon the structure or structures involved in the trauma. A septal lesion involving the bundle of His can produce heart block. If a leaf of the mitral valve is severed or if one of the chordae tendinae is severed, mitral insufficiency results. If a stab enters a cardiac cavity, bleeding may or may not occur. If the wound is small and enters obliquely into the ventricle, the wound will not emit blood. If a major coronary artery is severed, the ventricular wall supplied by the artery becomes ischemic and ventricular fibrillation occurs.

Diagnosis: The manifestations of penetrating cardiac injuries are variable. The clinical signs can be grouped as follows· (1) Those produced by injury of the intrinsic structures of the heart, such as a valve, a coronary artery, the conduction system, etc.; (2) those produced by exsanguination, and (3) those produced by compression of the heart. Severe injuries of intrinsic cardiac structures, as a rule, are immediately fatal and the problem of diagnosis is not presented. Generally in such accidents the ventricles are thrown into fibrillation and death is immediate. If the injury to the heart is less severe, the patient will continue to live after the accident and the problems of diagnosis and treatment are presented. In many of these patients the heart will show no evidence of intrinsic cardiac damage

The signs are entirely those of exsanguination or compression. The blood escapes into the pleural cavity, into the mediastinum, into the pericardial cavity, or through the wound to the outside. The signs of exsanguination need not be discussed.

Treatment: Only brief discussion of this subject can be given. Most of the patients who reach the hospital alive require operation. Occasionally, a patient with a stab wound recovers without operation. The body must be kept warm. If the circulation has stopped or if it is feeble, intravenous fluid should be given while preparation for operation is made. If the respiration has stopped and if the patient has lost consciousness, urgent heroic steps should be taken.

It takes but a few moments to expose the heart and release the compression. When the patient begins to breathe, an anesthetic must be given



FIGURE 5 Author's method for suture of stab wound of the heart. A suture is placed in the apex of the left ventricle This is held in the left hand and at the same time the left index finger is placed upon (not in) the wound. This stops the bleeding Sutures are placed on each side of the wound, the finger is removed and when this is done gentle traction is applied to these sutures to control bleeding The wound is then sutured

while the surgeon takes care of the wound. For the less urgent operations an anesthetic is given before the operation is started and mechanical respiration is an added safeguard. An exposure to the left of the midline is usually used. If the wound is in the right side an exposure to the right of the sternum is indicated. The pleural cavity is opened. The pericardium is opened and the blood clot is evacuated. This releases the compression and immediately the heart fills with blood

The first pulsations of the heart after release of the compression are more vigorous than normal, and the tasks of controlling the bleeding and repairing the wound must be met by the surgeon. The literature contains dramatic descriptions of the blood spurting, of the surgeon getting it in his eyes, of a foam rising up to cover the heart, of the patient regaining consciousness and moving on the table, of tearing the heart muscle when

the wound was plugged by a finger, of sutures tearing through the heart muscle, of exsanguination, of a life saved or a life lost.

The problems, difficult as they appear to be, can always be managed with satisfaction if a few facts are held in mind. Hemorrhage from a ventricle must be controlled by placing a finger upon and never in the wound. To keep the finger from slipping off the wound the heart is steadied by a suture in the apex. After the apex suture is placed and after the index finger is placed upon the wound, the urgency of the operation is over and time can be taken to carry out a satisfactory repair of the wound. Control sutures are placed on each side of the finger, crossed and held under moderate tension by the assistant. The finger is removed. There is no bleeding and permanent sutures are placed. The control sutures and the apex suture are removed (Fig. 5).

An auricular wound cannot be controlled by this method. It can be repaired easily by taking the margin of the wound in clamps, bringing the margins together and then suturing the wound. It is impossible to stop bleeding from an auricular wound by placing the finger upon the wound. A hemostat will crush and break ventricular wall but will not do this to auricular wall.

Complications such as foreign bodies and infections will not be discussed.

Nonpenetrating Wounds or Contusions of the Heart

These wounds are inflicted when the body falls from a great height or when an impact or heavy force is applied to the chest or upper abdomen. The commonest type of injury producing contusion of the heart is the steering wheel accident. Another type of injury producing contusion of the heart is the passage of a wheel over the chest or over the upper abdomen; an impact by a fist, by a golf ball or by a horse's hoof can produce a contusion of the heart. Any part of the heart can be bruised, any of the chambers can be ruptured, and any of the valves can be torn. Hemorrhage of variable degree occurs in the heart muscle when a contusive injury is received. Areas of hemorrhage, contusion and laceration may occur, not only at the site of trauma, but elsewhere in the heart. These areas of hemorrhage can be multiple. The heart can be bruised without fracture of sternum or ribs. Indeed, there may be no demonstrable evidence of injury to the chest wall.

Rupture of the heart can occur in several ways. It can be ruptured as a toy balloon can be ruptured in one's hand by the application of sudden severe compression. One would expect that a trauma of this nature would be more destructive if it should be applied at the end of diastole or at the beginning of systole, when the heart is filled with blood. One would also expect this trauma to be more destructive if it should be applied from the base of the heart toward the apex, so that the blood cannot escape as the heart is compressed.

The heart can be ruptured by breaking open the friable myocardium. This can occur even though the heart is emptied of blood. The heart can be ruptured by softening of the bruised area. Analysis of the literature shows that if the patient survives the first nine hours after injury the

chances of surviving the first week are better than his chances of surviving the second week. One would expect the greatest amount of softening of the injured myocardium to be present during the second week and this point should be given special consideration in the treatment of these cases so that such blowouts of the heart may be avoided Another mechanism by which the heart can be ruptured is by sudden distention with blood. This can occur when the blood is forcibly driven from the legs and abdomen as when the body is engulfed in a cave-in accident. Spontaneous rupture of the right auricle has occurred.

Incidence of Cardiac Contusions: In 1935 Bright and Beck[7] analyzed the literature on nonpenetrating injuries of the heart and found 152 instances of cardiac rupture, 11 instances of failure without rupture, and 12 instances of recovery. In the recovery group the diagnosis was based upon clinical manifestations. According to this analysis, it appears that when the human heart received a contusion, death was the rule and recovery was the exception. According to experimental data the heart can withstand an enormous amount of contusive trauma and recover. In the experiments, recovery was the rule and death was the exception. We can conclude from these data that the group of human cases in which recovery took place was much smaller than it should have been. *The clinical diagnosis of cardiac contusion is made too infrequently It is my belief that contusions of the heart are fairly common.* I believe they are of commoner occurrence than the penetrating wounds of the heart.

Symptoms and Diagnosis: Weakness coming on after the accident is the commonest symptom of cardiac contusion. When the contusion is produced experimentally there is a fall in arterial pressure but, as a rule, the fall in pressure is of transient duration In the less severe cases of contusion the weakness is momentary. The patient extricates himself from the wreck, sits down for a while and is then on his way. In cases of severe contusion the circulatory shock can be extreme The patient may be unconscious, the arterial pressure low and the skin cold and clammy Restlessness and air hunger may be present. Tachycardia is the rule but bradycardia is sometimes present. Hemorrhage in the region of the bundle of His produces heart block.

The heart sounds are distant and resemble the ticking of a watch. Auricular fibrillation, if it appears, is usually transient, but it can be permanent and disabling. Pericardial discomfort or pain is almost always present. It may be in the epigastrium or it may radiate into either arm Vomiting sometimes occurs The pain, as a rule, occurs immediately after the accident, but it can occur after a latent period. It can grow worse over a period of days or weeks following the accident. It varies from a discomfort or ache to a sharp anginal pain.

The electrocardiogram shows alterations from the normal. The Q-R-S complex shows slurring and notching. Deep Q waves, large T waves, high take-off of T and inversion of T were frequently encountered in experimental studies. In our experiments those deviations from normal usually disappeared in the course of four to six weeks. The electrocardiographic changes that are due to hemorrhage disappear after the blood is absorbed. Those that are due to destruction of muscle are permanent

The diagnosis of cardiac contusion not infrequently becomes a problem of patient *versus* insurance company. Some of these problems are extremely difficult to settle. For example, a man is thrown out of his seat in a train accident and strikes his chest against a seat. He dies a few hours later and coronary sclerosis is found at autopsy examination. A woman, who never had signs or symptoms of heart trouble, is thrown from the seat in a car accident. The lumbar muscles are bruised, but she does not know whether or not she struck her chest. Auricular fibrillation develops immediately after the accident. Later an embolus lodges in a femoral artery and the leg must be amputated. Did this patient sustain an injury to the heart producing auricular fibrillation or did the injury accentuate a cardiac lesion that was present but had not manifested itself, or was the injury entirely incidental?

Following is a brief summary of a case of cardiac contusion:

A delivery man for a bakery, twenty-five years of age, ran his truck into an automobile and demolished the front end of his truck. His chest was thrown forward against the steering wheel. He transferred his load of bakery goods into another truck and proceeded with the delivery. He worked the following day and experienced some upper abdominal pain. On the second day following the accident he experienced weakness and shortness of breath. He continued to work, but on the fourth day consulted a physician At that time he had dyspnea on exertion, pain in the chest, and a pulse rate of 120 per minute. Slight discoloration of the skin was found over the left seventh costal cartilage On the eighth day following the accident, he worked fourteen hours, but with great difficulty The next day he was unable to work. His symptoms were weakness, dyspnea, pain in the chest and pain down the right arm. He again consulted his physician He was in bed at home for seven days and in a hospital for ten days. He walked home and had to stop several times because of dyspnea and weakness Blood stained sputum appeared. The heart dilated and signs of failure appeared He died eighty-five days after the accident. Mural thrombi were found in the right ventricle and in the left ventricle Pulmonary emboli were found and these most probably originated from the mural thrombus in the right ventricle. The seventh costal cartilage was broken The heart wall directly beneath this cartilage had the thrombi The accident sustained by this patient was a steering wheel injury which produced myocardial contusion, cardiac weakness, dyspnea and pain, mural thrombi, pulmonary emboli, cardiac failure, and death.

Treatment: The symptoms can be transient and recovery rapid. Weakness and tachycardia may require rest in bed. I have observed the ventricles go from a rapid ventricular tachycardia to ventricular fibrillation following contusive trauma. If quinidine can prevent the development of ventricular fibrillation its use in indicated. Oxygen is indicated in the presence of dyspnea and cyanosis. Morphine and other sedatives should be used to induce rest and quiet.

Softening of the bruised muscle takes place especially in the second week and there is a danger of rupture of the heart. Exertion is to be avoided. Straining at the stool, coughing, etc., are to be avoided. Surgical intervention is indicated if rupture occurs. It seems that operation might have been feasible in some of the patients in whom death occurred from rupture. In some of these instances, the bruised area was not so extensive but that sutures could have been placed to close the opening in ventricle

or auricle. A graft of fascia lata or parietal pericardium can be placed upon the contusion to prevent rupture and the formation of an aneurysm of the heart. Up to the present time this operation has not been done on the human heart. We have repaired by suture rupture of the heart produced experimentally and we have reinforced the heart wall by free grafts. Perhaps these procedures can be applied to the human heart. The opportunity to do this operation is fleeting, but there are instances in which there is sufficient time to do the operation.

HEMOPERICARDIUM

Hemorrhage into the pericardial cavity occurs in the following conditions: Penetrating wounds of the heart and intrapericardial segments of the great vessels, contusion of the heart without rupture of the heart, contusion of the heart with rupture, spontaneous rupture of an auricle or ventricle, rupture of a myocardial infarct, rupture of an aneurysm of a ventricle, rupture of the base of a sclerotic aorta, tumor of the heart, scurvy, the hemorrhagic diatheses, rheumatic fever.

The hemorrhage can occur rapidly or slowly. It can be constant until death occurs or it can stop. It can recur. If the bleeding is slow or intermittent, a large quantity of fluid can be contained in the pericardial cavity because the pericardium stretches in response to the continued low grade pressure within.

The *clinical signs* and symptoms produced by an accumulation of blood or bloody fluid in the pericardial cavity vary with the rapidity of its formation Usually the signs of acute cardiac compression are produced, but slow and intermittent bleeding can produce the symptoms of chronic cardiac compression.

The *diagnosis* of hemopericardium is obvious in many instances. If the nature of the fluid is obscure, removal of fluid by aspiration is carried out. The thin bloody exudates are treated by aspiration rather than by operation.

The proper *treatment* requires nice judgment Repeated episodes of bleeding from the right auricle took place in a case reported by Clowe, Kellert, and Gorham. There was no history of trauma in this patient. Exploration and suture of the auricle was indicated in this condition in much the same way as in a penetrating wound of the heart that emits blood Mansell Moullin in a timely operation removed a blood clot from the pericardial cavity in a boy who received a nonpenetrating cardiac injury in a rugby game We should not be too conservative in performing operation for purposes of exploration. Sauerbruch, operating for a condition that he thought was a mediastinal cyst, opened into an aneurysm that came off the right ventricle. The thin walled sac could not be closed because the sutures tore out. He then inserted two fingers into the structure and plugged the communication with the ventricular cavity. Excision of the sac and closure of the ventricle were successfully accomplished.

PURULENT PERICARDITIS

Purulent pericarditis should be suspected in any patient who shows signs of either acute or chronic compression of the heart in the presence

of infection. It can occur as a complication or as a sequel to pneumonia, osteomyelitis, empyema of the thorax, throat infections, cholecystitis, appendicitis, peritonitis, etc. The infection can be introduced through a penetrating wound in the chest. It can be introduced with a foreign body like a fish bone or a needle from the esophagus. In some instances the infection is blood-borne.

Pus forms rapidly or slowly. Usually it develops so rapidly that the pericardium does not have time to stretch as it does in the sterile effusions or in the tuberculous effusions. The clinical picture is that of acute cardiac compression, but edema, ascites and enlargement of the liver can appear in a few days and the picture of chronic cardiac compression can develop.

As a rule the patient is acutely ill. The circulation is poor, the arterial pressure is low, the hands and feet are cold, clammy and cyanotic, and the patient is toxic from the infection. The presence of purulent pericarditis should be suspected in every patient who has an infection such as osteomyelitis or pneumonia and who is not doing so well as he should in consideration of the infected lesion. The pressure on the heart must be released and the pus must be evacuated if the patient's life is to be saved. This must be done as early as possible.

After the diagnosis of purulent fluid is confirmed by aspiration of pus, open incision and drainage are carried out. The operation should not be any more extensive than necessary. The anesthetic of choice is novocain. Inhalation anesthesia must be carefully given because the patient tolerates poorly any inhalation anesthetic drug. The left fifth or sixth costal cartilage is removed. The pericardium is opened and the margin of the pericardial incision is sutured to the skin. The pericardial cavity can be irrigated with warm physiologic solution of sodium chloride. Antiseptic chemicals, especially Dakin's solution, should never to used. Penicillin should be given. The pericardium cannot tolerate antiseptic solutions. Rubber tubes and drainage materials should not be placed in the pericardial cavity because of the possibility of erosion of a vessel. Occasionally a pocket of pus forms, but in my experience the cavity becomes obliterated without abscess formation and the wound heals. The incidence of purulent pericarditis has been greatly reduced by the antibiotics. These may be injected directly into the pericardial cavity.

A boy, aged six years, was admitted to the University Hospitals July 28, 1935, with fever, sore throat, labored respiration, and substernal pain. His illness began six days before admission with sore throat and stiffness of the neck. The cervical lymph nodes on one side became enlarged Two days later pain on breathing appeared beneath the sternum and respiration became shallow and labored The temperature was elevated. The lungs were clear. Upon admission to the hospital the patient was acutely ill. He was dyspneic and cyanotic. The extremities were cold The pharynx was slightly injected. The precordium was quiet and did not show any pulsation The heart sounds were distant and could not be clearly distinguished. There were no murmurs The area of cardiopericardial dulness was increased. The liver was tender and slightly enlarged The pulse rate was 120 to 130 per minute The pulse was thready and irregular. Respiration rate was forty-two per minute The systolic pressure was 86 mm. of mercury. The electrocardiogram showed slurring of

Q-R-S in all leads with deep S in Lead I T was upright in all leads and the S-T take-off was elevated in all leads

An aspirating needle was inserted into the pericardial cavity and 100 cc. of greenish-yellow thin pus containing type four pneumococcus was removed. The circulation immediately improved after this fluid was withdrawn, but the improvement was temporary. Aspiration was repeated on the following day with beneficial result, but the improvement was again temporary. Operation was carried out. Light nitrous oxide anesthesia was used. The left fifth costal cartilage was removed The internal mammary vessels were ligated above and below. The pericardium was incised Fluid spurted about 20 cm from the wound Three hundred cubic centimeters of pus were removed The heart was covered by fibrin. The pericardium was sutured to the skin Marked improvement in the condition followed. The following quotation was taken from my operative note,—"This child represents a type of cardiac compression which is intermediate between the acute and chronic stages It is acute in that the arterial circulation is markedly impaired and the veins are not enlarged. It is chronic in that the liver is enlarged and edema is present in the scrotum and ankles." Empyema of the left chest and subcutaneous abscesses developed Improvement followed drainage All wounds healed and the patient was discharged from the hospital October 26, 1935. The liver became smaller The temperature was normal and there was no evidence of infection

January 8, 1936, the child was readmitted to the hospital for study. He showed slight evidence of chronic compression of the heart On the venous side of the circulation were the following manifestations of stasis—subcutaneous edema, ascites, pleural effusion, each of slight degree Cyanosis, enlargement of the veins and enlargement of the liver were absent On the arterial side was a systolic pressure of 85 mm of mercury and a diastolic pressure of 50 mm of mercury. The heart sounds were normal

On June 11, 1936, the patient was readmitted for study The arterial pressure was 78 mm. of mercury systolic and 60 mm of mercury diastolic. The venous pressure was 15 cm of water. The liver was slightly enlarged Slight edema of the ankles was present. The precordium was quiet The cardiopericardial shadow was becoming smaller The heart was becoming compressed by the contracture taking place in the scarified pericardium The degree of compression became more marked during the next six months—a condition that anyone who is familiar with the chronic compression triad could recognize in a moment and recognize by inspection alone without any of the special tests

He had (1) a quiet heart as shown by inspection of the precordium; (2) increased pressure in the superior vena cava as shown by inspection of the enlarged veins in the neck and arms and cyanosis of the capillary bed in the nails, and (3) increased pressure in the inferior vena cava as shown by inspection of the swollen ankles and swollen scrotum and enlarged abdomen All other manifestations were secondary to these three primary components of this disease triad. As a rule, the heart is normal before it becomes compressed Compression, being an extrinsic disorder, should not produce murmurs The compressed heart is efficient although it is not adequate to meet the requirements of a normal intake and output. It does not waste energy. It undergoes atrophy of disuse. The x-rays showed a progressive diminution in the size of the pericardial shadow during the preceding year. The heart was not fixed in position. The electrocardiogram showed low voltage and slurring of Q-R-S complex. The diastolic-systolic excursion was reduced (Fig. 4*A*) The veins were distended. Pulsus paradoxus was present. The pulse pressure was 20 to 30 mm of

mercury. Ascites was present. The liver was enlarged Subcutaneous edema of ankles and scrotum were present

Operation December 3, 1936. The scar was two to three millimeters in thickness, intimately adherent to the heart. Sharp dissection was necessary to separate it from the heart Separation was carried out over the anterior and lateral surfaces and the scar was excised. The heart dilated after this was done, indicating that the compression was corrected. The child made an execllent recovery. The cyanosis disappeared The venous pressure was normal. Ascites and edema disappeared The liver became smaller. The diastolic-systolic excursion of the heart improved and the pulse pressure increased This patient is now twenty-six years old and has no cardiac symptoms.

CARDIAC COMPRESSION DUE TO SCARS

Etiology: The compression scars are always extrinsic in origin. They never develop as a sequel or complication of an intrinsic lesion. They never originate from rheumatic heart disease. The infection finds entrance into the pericardium from the pharynx, lungs, pleura or mediastinum. However, Dakin's solution and other chemical irritants applied to the normal pericardium of animals result in scars that later undergo contracture and produce compression of the heart. In my series of operated cases, seven showed evidence of tuberculosis in the scars and thirty did not show evidence of tuberculosis in the scar removed at operation. Two of this group of thirty patients, however, had tuberculosis elsewhere without showing tubercles in the scar.

Diagnosis: The author's triad makes the diagnosis of chronic cardiac compression simple and infallible (Fig. 3). Usually the diagnosis can be made by inspection alone. The ascites is apparent; the distention of the venous system is apparent and the quiet precordium is readily observed. Our understanding of cardiac compression has been greatly simplified by placing proper emphasis upon the compression and by eliminating the old terminology of adhesive pericarditis, Pick's disease, mediastinopericarditis and constrictive pericarditis, together with the implication that the heart undergoes dilatation, hypertrophy, and failure because it pulls upon adhesions. That the compressed heart is entirely free from these assumed disturbances even though adhesions are everywhere present has been demonstrated beyond any reasonable doubt.

Differential diagnosis, as a rule, is not a problem. Obstructions elsewhere at the triscupid valve, at the pulmonic valve, at the pulmonary artery, at the mitral valve, at the aortic valve and the aorta have characteristics that make the localization of the obstruction at these sites possible. I have seen several patients with the obstruction in the pulmonary bed due to chronic pulmonary infection and fibrosis with narrowing of the smaller vessels in the pulmonary bed. These patients showed the signs of stasis in each vena cava with ascites and cyanosis, but the heart made a normal diastolic-systolic excursion. In the absence of a quiet heart the diagnosis of compression was not made and the fibrotic appearance of the lungs placed the obstruction in the lungs.

Compression of the heart due to scar is to be differentiated from compression due to other agents, such as fluid in the pericardial cavity, blood

exudate, transudate or a neoplasm. The size and contour of the x-ray shadow helps here. If fluid is suspected aspiration might be carried out before operation is done. In several of my patients the compression was due to a combination of fluid and scar.

The compressed heart is always small. The small atrophic condition of the heart may or may not be suggested by the x-ray shadow. Scars vary from one to about ten millimeters in thickness and a thick scar can give the atrophic heart the appearance of being either normal or enlarged.

Preascitic Compression Scars: When the venous pressure is greater than 20 cm water, fluid filters out of the vascular bed into the abdomen producing ascites. When the pressure is less than this level ascites does not develop. On the basis of this, one would expect mild forms of compression without ascites and these cases do exist The venous pressure is 14 to 20 cm. water. The heart does not fill normally and the circulation is slowed by this mild compression of the heart. The symptoms are mild but it is possible to recognize this condition. I operated on several patients who had this condition and these patients were cured

Operation for Removal of Compression Scars: In the past it was believed to be desirable to delay operation until the infectious process subsided as indicated by the temperature of the patient. The antibiotics have changed this attitude and operation can be carried out earlier in the course of the disease. The patient is given a course of vigorous treatment with appropriate antibiotics and the agents that are effective in tuberculosis. Holman and Willett[6] reported eight patients with tuberculous pericarditis and in six of whom viable tubercle bacilli were cultured These patients recovered from operation and were well The patient is dehydrated before operation. Fluid is aspirated from the abdomen and chest if there is a considerable amount present. The patient is digitalized before operation Light anesthesia is used. Respiration should not be depressed by drugs. My anesthetist uses a small amount of pentothal, then introduces an intratracheal tube and carries the patient along with light ether anesthesia and relaxant drugs. I use the Rand-Wolfe respirator for all cardiac surgery and I think it is a great aid The anesthesia is such that the patient should be breathing on his own and awake as the dressing is applied to the incision. The patient is placed in slight Fowler's position for operation. The left arm is extended. The incision is made between the third and fourth ribs and cartilages extending from the left border of the sternum to the midaxillary line. The chest should be draped so that the incision can be extended across the sternum to the interspace on the right. The exposure of the heart is much better if the sternum is cut across and retracted. In the past I seldom cut across the sternum but now I recommend it. The mammary vessels are securely ligated before they are cut. The left pleural cavity is opened and if necessary the right pleural cavity is also opened. If both cavities are opened then a drainage tube is placed in each cavity before the wound is closed. The left phrenic nerve and the vessels accompanying this nerve are dissected carefully from the pericardium and retracted away from the operative area. The scar is then incised and the proper plane is found between scar and heart. As a rule this is done without difficulty but occasionally it is possible to cut into the

heart or cut a coronary artery. One must be ever mindful that the coronary arteries may be cut or compressed by the finger. I lost one patient from pressure on an artery which fibrillated the heart and at that time there was no method for defibrillation of the heart. The scar is dissected by sharp or blunt dissection, a little at a time. Transverse cuts in the scar open it up so that you can do this dissection with less difficulty. As much scar as possible is removed but it is not necessary to remove it posteriorly where it is almost impossible technically to remove it. There is a limit to the amount of dislocation that the heart can tolerate. The base of the heart should be carefully freed of scar including auricles, aorta, pulmonary artery, and the venae cavae. Sometimes you can observe where the scar does most of its compression and it is great satisfaction to remove scar from these areas and observe result. I recommend frequent rest periods for the heart during which the lungs are nicely inflated and nicely deflated. The lungs must not be too forcibly inflated nor should they be continuously distended. They should come up nicely and go down nicely with each cycle of the respiration. If an accidental cut or tear is made in any of the cardiac structures it, of course, must be repaired. As a rule, with good exposure, this can be repaired without difficulty. If the rate goes up to 120 or higher per minute, I recommend cedilanid be given intravenously. This is a digitalis preparation which can be given intravenously and is a very important drug in all types of cardiac surgery.

Results Obtained after Resection of Compression Scars: The results in my cases up to 1949 were analyzed.[7] There were seventy operations on sixty-four patients. There was one operative mortality from ventricular fibrillation referred to above, 1.5 per cent. In the postoperative period there were five from tuberculosis, five from other causes, for a total of 15.7 per cent. Two of these were due to infection and three were due to acute dilatation of the heart. Perhaps the acute dilatation could have been taken care of by blood-letting. Deaths over a period of eighteen years were 5 or 7.8 per cent. These five patients were improved insofar as compression was concerned. One developed miliary tuberculosis and died several months later; one developed pneumonia several years later; one developed recurrence of compression and died several years later, and two died of unknown causes. There were forty-eight living patients or seventy-five per cent and of these there are forty-six complete cures and two with some recurrence but who were improved. Operation was not refused a single patient because of seriousness of physical condition. An analysis of my cases was reported by Chambliss and associates.

Heuer and Andrus reported nineteen operations done on eighteen patients over a period of eight years. Of these seven were cured; three recently operated upon were improved and probably cured; five were improved but not cured; and four were not improved. Cure was obtained in fifty-five per cent of the patients. Harrington operated upon twenty-four patients. Of these five died in the hospital. There was one operative [illegible] three due to cardiac failure. Of [illegible] cured and nine were improved [illegible] patients.

THE PATENT DUCTUS ARTERIOSUS

In 1907 John Munro suggested that the ductus arteriosus might be ligated if it remained patent. There appears to be no record of an attempt to perform the operation until 1937 when J. W. Strieder recorded an unsuccessful attempt to ligate the structure in a patient who had bacterial endocarditis. John Hubbard selected the first patient upon whom the ductus was successfully ligated by Robert Gross.[8]

Figure 6 illustrates the shunt in the circulation produced by this communication. In this condition blood flows from the aorta where the pres-

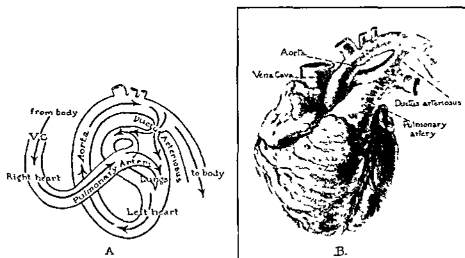


FIGURE 6 *A*, Diagram of circulation showing the short circuit of blood through the patent ductus arteriosus *B*, Heart of a child three days old illustrating patent ductus arteriosus (Nelson Loose Leaf Surgery, 1927—ten years before the first operation)

sure is relatively high into the pulmonary artery where the pressure is lower. A part of the oxygenated blood in the aorta is returned to the lungs and a short circuit is thus set up. This shunting of the blood stream is followed by certain complications. In the first place the heart has increased work placed upon it. The left ventricle dilates and undergoes hypertrophy in a manner similar to that seen when a fistula connects any large artery and vein as in the femoral region or in the neck or axilla. The right ventricle also works against an increased resistance in the pulmonary bed. Endocarditis may develop at any time in a patient with a patent ductus arteriosus. Growth and nutrition can be affected by the condition and it would appear that the wall of the ductus is sometimes thin and may rupture.

Selection of Patients: The indications for operation have become liberalized as surgeons gained experience in performing the operation and as the risk of doing the operation has fallen. The opportune age for operation is four to six years but it has been done soon after birth in the presence of heart failure and it also has been done in late adult life. As a rule the

operation is indicated when the diagnosis is made. Sometimes there are no symptoms because the patient having been born with this lesion has never experienced normal health and activity.

The Operative Procedure: Several types of approach have been used. Adequate exposure is necessary if the duct is to be dissected free and section of the duct carried out. The writer uses a transverse incision below the left breast extending from the sternum laterally to the posterior axillary line. The position on the table is such that the midportion of the incision is uppermost. The pectoral muscle is cut parallel to the skin incision and retracted upward. An intercostal incision is made between the third and fourth ribs. A self retaining retractor is placed and the chest is opened for a distance of about 15 cm. The pleura just superior to the hilum of the lung is cut along the vagus nerve. The recurrent laryngeal nerve is identified and the duct is dissected free. Sharp dissection is used and a word of warning is given not to use blunt dissection as it may tear the duct, pulmonary artery or aorta. Dissection beneath the duct is facilitated by a ball-dissector which presents the tissue posterior to the duct so that it can be cut. This ball-dissector is a ball of metal 4 mm. in diameter on a handle shaped like a cane. When placed beneath the duct the tissues are presented so that they can be cut. Special clamps are placed on the aortic and pulmonic ends. Ordinary clamps crush these vessels and should not be used. Pott's clamps are excellent for this purpose. The duct is transected between clamps and each end is sutured by a No. 5 deknatel arterial suture. The technic that I use is a continuous mattress suture for the first line and then come back to the starting point with an over-and-over continuous suture. If there is any bleeding when the clamps are removed an additional single or mattress stitch is applied. Some surgeons dissect the aorta free and approach it laterally. There are no intercostal arteries at this level. I have never used this approach but if hemorrhage is encountered it is well to bear in mind that if the aorta is dissected free a clamp can be placed across the aorta but parallel to the aorta so as not to occlude it and the bleeding point controlled. I know of one instance in which the aorta was clamped across and this was followed by paralysis of the legs The Potts clamp or the Beck aorta clamp will obviate this danger of transverse clamping These clamps are applied in the longitudinal direction of the aorta. Hemorrhage can be troublesome. If the dissection appears to be too hazardous it is advisable to ligate the duct. Two ligatures of narrow umbilical tape are used together with one or two ligatures of silk. The possibility of recanalization is slight.

It is not advisable to suture the pleura over the vessels because if the pleura is closed it may obscure any bleeding from these structures. The writer operated upon a patient in whom the pericardium came up over the duct and it was opened. Several hours later the patient was in circulatory shock but only a small amount of blood had come out of the drainage tube in the chest. The heart stopped beating as the incision was opened. The pericardium was filled with blood and the patient had acute compression of the heart. The heart was resuscitated. The bleeding had come from a needle hole in the aorta and the blood entered the pericardium through the small opening made at operation.

Gross reported a series of 568 patients in whom the duct was divided and sutured. The mortality was 1.7 per cent.[9] In a series of 143 patients operated upon by the writer the mortality was 1.4 per cent.

Patent Ductus Arteriosus with Reverse Flow: This occurs in patients with pulmonary hypertension when the pulmonary pressure exceeds aortic pressure. When the pressure is the same in each of these vessels there may be no flow through the duct and the flow may change or reverse itself as the pressures change. Reverse flow produces cyanosis of the lower extremities while the hands, head and neck are pink. If there is no flow through the duct it is possible to clamp the duct, cut the duct between clamps and suture each end. Following this procedure the pressure in the pulmonary artery has a tendency to fall to more normal levels. When pulmonary artery pressure is higher than aortic pressure it is hazardous to divide the duct because of the possibility of right heart failure Reverse flow due to pulmonary hypertension is accepted as a contraindication to operation. Reverse flow is sometimes associated with other cardiac abnormalities such as pulmonic stenosis, septal defects, tricuspid atresia, and transposition of the great vessels.

TETRALOGY OF FALLOT

The "blue baby operation" has received considerable attention due to the contribution by Blalock[10] and Taussig, Potts,[11] Brock[12] and others. The term tetralogy of Fallot is generally applied to this lesion under discussion because Fallot in 1888 described it. However, Landifort in 1777 and Hope in 1842 also described it. The essential features of this lesion consist of atresia or stenosis of the pulmonary artery, dextroposition of the aorta, ventricular septal defect, and right ventricular hypertrophy. The features of this defect that concern us most are (1) an inadequate amount of blood to the lungs and (2) a large amount of venous blood in the aorta. The point of practical importance is to deliver some of the aortic blood to the pulmonary artery so that it can become oxygenated. Blalock accomplished this by turning a systemic artery—subclavian or carotid—into the pulmonary artery. Potts took a step farther and made direct anastomosis between aorta and pulmonary artery. These have been phenomenal developments. They have brought to light more blue babies than anyone thought existed In a short term of a few years about 1000 of them have been operated upon. The operation is beneficial. Improvement is marked although it should be stated that the operation does not completely correct the various defects. It adds another defect but a beneficial defect—a patent ductus—to those already existing.

The clinical features are cyanosis and clubbing, a heart of normal size, usually a murmur at the base, and a pure second sound. The electrocardiogram shows right axis deviation. The x-ray shows absence of the normal fulness of the pulmonary conus and clear lung fields. Fluoroscopy shows no pulsations at the hilar regions of the lungs. There are many variables. The oxygen saturation of arterial blood may vary from eighty-eight to ten per cent. The exercise tolerance of the individual shows marked variation. Operation is indicated for those who are severely handicapped. Fig. 7 is a photograph of Dr. Blalock.



FIGURE 7 Alfred Blalock (1899-) whose shunt operation for tetralogy of Fallot did so much to stimulate the development of cardiac surgery.

Selection of Patients: The operation is indicated only in cases in which the primary difficulty is lack of circulation to the lungs. Operation is possible only provided a pulmonary artery is present. The pressure in the pulmonary artery must be lower than the pressure in the systemic artery. The heart must be able to tolerate the altered circulation. The heart should not be enlarged. There is no fulness of the pulmonary conus and no pulsations in the lung fields. Usually there is absence of hilar shadows. However, in patients with extensive collateral circulation these shadows may become pronounced but are composed of an aggregate of fine shadows and never show expansile pulsations.

The operation is indicated in patients in whom cyanosis is present and inadequate amount of blood enters the pulmonary bed. The admixture of blood is due to the over-riding of the aorta with a septal defect beneath the aorta. The aorta is considerably larger than the pulmonary artery and drains a large part of the blood from both ventricles. In some instances the pulmonary artery is also narrowed and smaller than normal. There may also be infundibular or valvular stenosis at the pulmonary out-flow tract. If there is a valvular stenosis present, it is advisable to release this stenosis rather than carry out the shunting operation. The opportune time for the operation is the age of four to six years, although it has been done in the newborn and it has been done in adults. The presence of cyanosis and the reduction of pulmonary markings are indications for operation

The Blalock-Taussig Operation: The reader is referred to the original papers by these authors. This operation is anastomosis between a systemic artery and pulmonary artery. The most desirable artery is the subclavian coming off the innominate but the innominate artery being only on the right side, this favorable anatomical relationship can only be used when the approach is on the right side of the chest The writer uses the left sided approach in all cases. The left chest is opened between the third and fourth ribs. The pericardium is opened transversely in order to examine the pulmonary artery and the region of the pulmonary valve and the infundibular area of the right ventricle. If a valvular stenosis is present, the operation of choice is valvulotomy rather than placing a shunt. Other advantages of opening the pericardium and exploration of the pulmonary artery is in the fact that the pulmonary artery may be so small that it may be difficult to find the artery as it penetrates the lungs With the pericardium opened the location of the pulmonary artery coming into the lung can always be determined. The pulmonary artery is dissected free as it enters the left lung. The left subclavian artery is also dissected free up to the point where it breaks up into several branches. It is then determined whether or not the subclavian artery will be long enough to breach the gap between the aorta and pulmonary artery In some cases every millimeter of length is necessary in order to establish a satisfactory flow. In some instances the artery is too short to make a circular turn around the aorta down to the pulmonary artery If there is any tension, the artery should not be turned down for this purpose. If it is too short then an alternate procedure should be carried out as described below. If the length of the

artery is adequate, it is then cut across as far distally as possible. It is then turned down and sutured end to side into the pulmonary artery. Number 5 deknatel suture material is used for this purpose. The suture may be either everting or an ordinary over and over suture. There are special clamps which can pinch off enough of the pulmonary artery to open it without occluding it. These clamps possess a handle, steady the artery without occluding it and facilitate anastomosis. Experience has shown that the subclavian artery is about the proper size for the shunt in all patients with tetralogy. In children the lumen of the artery is small and the shunt must be small. In adults the artery is larger and the shunt can be larger.

As a rule the results of the operation are very satisfactory. The color becomes pinker, the blood becomes thinner, the clubbing of fingers and toes begins to disappear, and the patient becomes stronger and more active. Even though the anatomical defect in the heart has not been corrected, some of these patients have led almost normal lives. Several of my patients have gotten married and have had children and others have been able to support a household. Occasionally as the patient grows in size, tension develops on the subclavian artery and the shunt becomes occluded. The murmur disappears, the previous symptoms return, and when this occurs a new shunt should be placed.

The Potts-Smith-Gibson Operation: This operation consists of direct anastomosis between aorta and pulmonary artery made possible by a special clamp which enables one to open the aorta without producing complete occlusion of the aorta. This operation accomplishes the same purpose as the Blalock-Taussig operation. It has two advantages in that a systemic artery is not sacrificed for the anastomosis and the operation has a lower mortality rate. In this operation the side on which operation is done is determined by the position of the aorta. With a left arch the aorta comes down on the left and lies close to the left pulmonary artery. With the aorta on the right side the operation is done on the right side.

Potts originally made an opening in the aorta of 5/16 inch. More recently he reduced this to 4/16 inch. The opening can be made too large especially in small children. The writer lost two young infants from pulmonary edema which he attributed to the size of the stoma in the aorta. In small infants the stoma should not be larger than 4/16 inch and perhaps it should be slightly smaller. The suture used is an over and over continuous suture. It is remarkable that clotting does not take place at the site of the anastomosis in either operation. This is due to the rapidity of blood flow through the anastomosis, the systemic artery and aorta carrying a considerably higher pressure than the pulmonary artery and the blood washing away platelets and fibrin that tend to adhere to the suture line

Free Graft Between Aorta and Pulmonary Artery: This operation was developed by the writer in 1948 and has not been published. It consists in placing a free graft of fresh artery or vein between the aorta and the pulmonary artery. In small children the segment of vein is taken from one of the parents. In adults an autogenous segment of vein is used. When a

free graft is not available at operation, a segment of subclavian artery may be taken. As a rule the free graft need not be longer than 1 or 2 cm. to bridge the gap between the aorta and pulmonary artery. This operation is used in those cases where the subclavian artery is too short and also those patients in whom direct anastomosis cannot be made. In children the stoma in the aorta should be 3.5 mm. In adults it should be 4.0 mm. A special instrument is available to punch out a circular piece of aorta. A Beck clamp is placed on the aorta. The aorta is opened for several millimeters. A punch is introduced in the opening made in the aorta. The graft is then sutured to the aorta with an over and over suture. A similar procedure is used on the pulmonary artery. After the operation is completed it resembles a patent ductus arteriosus. The graft lies in a good position to remain patent. There is probably also some advantage in using a graft to avoid making too large a shunt as may occur in direct anastomosis without a graft.

DIRECT APPROACH TO PULMONARY STENOSIS

This form of treatment was introduced by Brock and consists in the direct attack upon the stenosis. An instrument is inserted into the right ventricle and directed into the area of stenosis. If the stenosis is valvular, the ring is cut and dilated by special instruments. If the stenosis is infundibular, then some of the muscle on the cardiac side of the pulmonary valve is cut and removed by special instruments The direct approach has much to recommend it. Brock reported 140 cases operated upon by this method. Valvulotomy was done in fifty cases with good or very good results in seventy-four per cent, improvement in twelve per cent, no improvement in two per cent, and a mortality of twelve per cent. Infundibular resection was done in sixty-two cases with eighty, seven, zero, and thirteen per cent respectively, and in twenty-eight cases infundibular resection plus valvulotomy were done with results of seventy-two, twenty-one, zero, and seven per cent respectively. The total mortality was 11 5 per cent These results are to be compared with those by Blalock and Taussig. In 857 cases reported by them the results were good or very good in eighty per cent, improvement in three per cent, no improvement in two per cent, and a mortality of fourteen per cent. On the basis of these figures there is not much difference in the results obtained by the shunt operation and by the direct approach. Each operation has its place, each can produce a good or excellent result but the writer believes the tendency is towards the direct approach The writer has had patients who were relieved by a shunt for several years, then the degree of improvement became less. The direct operation in these patients produced an excellent result.

After the stenosis is released the patient is left with a ventricular septal defect and surgery is now approaching a stage where even these defects are being closed by open heart operation.

COARCTATION OF THE AORTA

Coarctation of the aorta is a congenital condition in which the aorta is narrowed or completely obstructed This narrowing of the aorta produces

an elevation of arterial pressure proximal to the obstruction and a reduction of arterial pressure distal to the obstruction. There are two types of coarctation. One is a localized narrowing of the aorta in the distal arch usually at or beyond the remnant of the ductus arteriosus. The other type is a generalized narrowing of the aorta anywhere along its course.

The final effect of coarctation upon the individual is indicated by a survey of autopsy material carried out by Reifenstein, Levine, and Gross. According to this survey there were four types of end-result and each group was approximately the same size. These groups were as follows: (1) patients in whom there was little or no disability and in whom the coarctation was not related to the cause of death; (2) patients who died of bacterial endocarditis or aortitis; (3) patients who died of rupture of the aorta; (4) patients who died of cardiac failure or intracranial hemorrhage.

Infection was most common in the third decade, rupture of aorta or cerebral artery was most common in the second and third decades, and failure was most common in the third, fourth, and fifth decades. The average life span was thirty years. Coarctation is a serious condition. Fortunately many of these conditions can be cured by operation.

Clinical Manifestations: The arterial pressure in the arms is moderately or markedly elevated. Exercise brings forth a greater rise than normal. A difference of pressure in the two arms of more than thirty to forty mm. of mercury (Gross) may be suggestive evidence of the location of the coarctation as proximal or distal to the origin of the left subclavian artery. The pressure in the legs is reduced. Femoral pulse may be absent. Collateral circulation between the high and low pressure beds develops by way of the internal mammary arteries and in the intercostal arteries. Pulsation in these vessels is increased and can often be palpated. The intercostal arteries sometimes erode the lower border of the ribs as shown by x-rays The murmurs heard are variable. Complete obstruction of aorta, like complete ligation of a major artery, is silent. Partial obstruction produces a murmur which can be heard between the scapulae, in the neck, and over the base and sometimes the apex of the heart. Murmurs may originate from other defects in the heart and great vessels and possibly also at the origin of greatly dilated branches coming off the aorta. The heart may be enlarged and hypertrophic. X-rays, taken in the proper plane in which the aortic shadow is away from the vertebrae, may indicate narrowing of the aortic knob and descending aorta Usually such evidence cannot be obtained. X-rays may show notching or scalloping of the inferior border of the ribs in their posterior and lateral portions. The upper three ribs do not show such changes. Visualization of coarctation by injection of diodrast into the aorta is not recommended. There have been a number of serious complications attending this study and the dangers are greater than the value obtained by visualization.

Operation: For the history of the surgical development of the treatment of coarctation, reference is made to articles by Crafoord and Nylin,[13] Gross and Hufnagel,[14] Clagett,[15] and Blalock and Park.[16]

The left chest is opened widely by a long incision between the third and

fourth ribs. It is not necessary to remove a rib nor to cut them posteriorly. The pleura over the aorta is incised and the aorta is dissected free over a distance of about 6 to 8 cm. Adequate mobilization of the aorta is essential. Usually the coarctation lies distal to the left subclavian artery. As a rule there are no small branches coming off the aorta in this dissection proximal to the coarctation. The ligamentum arteriosum is dissected free, clamped, cut, and each end sutured. The aorta distal to the coarctation gives origin to the intercostal arteries. These are variable in number, size, and position. Any of these arteries that arise from the aorta within a centimeter of the coarctation are ligated and cut. Dissection of the aorta is carried distally and an area is found between intercostal arteries large enough for application of the distal clamp. Any arteries proximal to the distal clamp are temporarily occluded. After dissection has been completed, a non-crushing clamp is applied proximally and distally to the coarctation. The clamps used are either those of Gross or straight or curved clamps of Potts. The Crafoord clamps are sometimes useful The left subclavian artery should not be occluded by the proximal clamp if this is possible. The narrowed area of the aorta is then excised by a heavy, sharp, straight scissors, which will make a clean cut. The cuts should be on the bias and should be parallel to each other both above and below so that the suture line, after it has been made will have a large diameter after the two ends are brought together. The narrow segment is removed. A series of interrupted mattress sutures is then placed beginning in the posterior area of the aorta. After this row of sutures has been placed, the two ends of the aorta are brought together by the assistant who supports the clamps As a rule this can be done without difficulty. Each suture is then tied. Ten or twelve interrupted Lembert sutures are then placed in the everted cuff of the aorta. As a rule it takes fifteen to twenty minutes to place these sutures and tie them. The distal clamp is then removed. Usually there is no bleeding but an additional suture may be necessary if there is bleeding. The proximal clamp is then removed. Any clamps on intercostal arteries are removed. The pleura is sutured over the aorta. The lungs are re-expanded and a drainage tube is introduced into the chest

In the writer's series of fifty cases, only one required a graft. The graft may be a sleeve of nylon of proper size or a homograft of an aorta. After the aorta is properly mobilized a section measuring 2.5 cm. can be removed without grafting It is advisable not to use a graft unless a direct anastomosis does not seem to be possible. Gross reported 19 of 180 patients operated upon in whom he used a graft but it is obvious from the illustrations of these patients that a graft was not necessary in each of these patients.

Results of Operation: The surgical procedure for correction of coarctation has improved with accumulation of experience. The procedure of choice is direct end to end anastomosis without a graft whenever this is possible.

In a series of fifty consecutive cases by the writer, direct anastomosis was possible in forty-nine and a graft was necessary in one. In 180 cases

by Gross a graft was used in nineteen or about ten per cent. There were two deaths in the writer's fifty cases, or four per cent. One was due to necrotizing arteriolitis of the abdominal organs. Three other similar complications have been reported by others. One death was due to dehiscence of the aortic suture line about two weeks after discharge from the hospital and was due to infection. In 270 patients by Gross the mortality was seventeen or six per cent but in the last 100 the mortality was two per cent.

The blood pressure usually falls after the anastomosis has been completed and the clamps have been removed. There are patients, however, in whom hypertension persists after operation and in one of the writer's

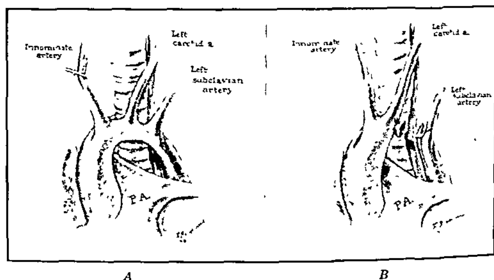


FIGURE 8 *A*, Double aortic arch with trachea and esophagus between the anterior and posterior portions of the aorta These structures were compressed *B*, The anterior portion of the double arch has been ligated and divided, thus relieving tracheal obstruction.

patients a cerebral hemorrhage occurred several days later from which he recovered. The pressure in the arms falls to normal in a week or two in eighty-eight per cent; in ten per cent some reduction occurs and in two per cent there was no reduction (Gross).

CONGENITAL MALFORMATIONS OF AORTA

Certain malformations of the aorta and its branches may compress trachea and esophagus and produce dysphagia, wheezing respiration, stridor, retraction of the chest, cough, and pulmonary infection. These symptoms may be severe. Compression of esophagus and trachea can usually be visualized by x-ray and fluoroscopic examination. Angiocardiograms may visualize the aorta and its branches. The trachea and esophagus are encircled by the double arch. One arch is usually larger than the other. In Group I the aorta comes off the heart in its normal position. The double arch

extends from right to left, one part behind and one part in front of esophagus and trachea. The arches join together to the left and give rise to the descending aorta. The ligamentum arteriosum lies on the left between pulmonary artery and aorta just beyond the origin of the subclavian artery. The malformations of Group II are mirror images of Group I. The aorta arises to the left of trachea and esophagus, one arch lies in front and one behind these structures. The arches join together to the right of esophagus and trachea to form the descending aorta which lower down crosses to the left side. The ligamentum arteriosum is attached to the right pulmonary artery and aorta just beyond the origin of the right subclavian artery.

It is possible to relieve some of these obstructions by ligation and section of the anterior arch (Fig. 8). In some cases section of the ductus arteriosus either alone or in conjunction with the section of the arch gives relief.

REVASCULARIZATION OF THE HEART FOR CORONARY ARTERY DISEASE[17,18]

Introduction: This subject has been investigated by Beck and his associates since 1932 and over 5000 experimental operations were done on the coronary blood vessels of the heart. This work has established a new line of thought on this subject. It is reasonable to state that the coronary problem now can be defined with better understanding and this promises to bring about more effective treatment.

Many avenues of approach to this problem have been investigated by these workers. Many of these, as has been the experience in all research, contributed little to our knowledge but it was necessary to investigate them. Certain facts have been established and from our present point of view these seem to have an enduring nature and will lead to better understanding in the future. Certainly there will be no progress in the treatment of coronary artery disease if our thinking does not change. Except for the anticoagulants *the attitude of the profession towards this disease has been* static and unrewarding. No segment of the profession has earned respectability for what it has been able to do in the treatment of this disease. The treatment consisted of sedation, rest, oxygen, and pills and there is no evidence that any of these medical measures add or subtract a single drop of blood to ischemic myocardium. Change in this attitude is a requirement The old must yield to the new.

Definition of the Problem:[19] There are two aspects to this problem. One concerns the total amount of blood available to the myocardium and the other concerns the distribution of this blood to every part of the myocardium. The capacity of the coronary arteries to carry blood is many more times as much as the capillary bed accepts and needs. In severe disease the lumina of the coronary arteries sometimes are so narrowed that one wonders how the heart could beat with so little blood. On the other hand there are instances in which the heart showed only slight arterial

stenosis and no myocardial infarct and one wonders why the heartbea was destroyed.

About ten per cent of the victims of the disease die from what we call "muscle death." There is insufficient blood entering the heart to preserv the beat and failure develops. Little or nothing can be done by operatio for this group of patients. The other ninety per cent of the patients di from an uneven distribution of the blood that gets into the heart. Ther is enough that gets in but it is *not evenly* distributed and this unever distribution leads to the production of electric currents which destroy the coordinated beat. This type of death we refer to as "mechanism death." According to Yater and associates, one-third of all victims of the disease have no infarct, old or recent. Much can be done to help these patients by operation.

The Stable and Unstable Heart:[20] An even distribution of oxygen to the heart produces electrical stability; an uneven distribution produces electrical instability. A uniformly pink heart is stable; a uniformly cyanosed heart is stable; a pink heart containing a cyanosed area is unstable and a cyanosed heart containing a pink area is unstable (Fig. 9). Stability is not related to the supply of oxygen delivered to the heart because oxygen can be cut off for minutes and the deeply cyanosed heart remains electrically stable. When differences in oxygen content are created experimentally, then electrical currents are produced which can destroy the coordinated mechanism. These differences can be produced in the pink heart and in the cyanosed heart. These currents are responsible for the vast majority of deaths from this disease. These deaths are not due to inadequate blood supply *nor* are they due to destruction of myocardium. They are due to electrical currents in the heart and this heart without these currents would not fibrillate and could keep on beating for years. The major emphasis, therefore, in the treatment of this disease should be placed upon these currents, which in turn are related to the distribution of blood. When the distribution of blood in the heart is even then these currents do not develop and the heart is in a good position to sustain one arterial occlusion after another until the inflow is reduced to such a level that the beat can no longer be sustained and the patient dies in failure.

An Axiom in Coronary Artery Occlusion: The fate of the patient depends upon the amount of blood available to the muscle beyond the occlusion. This is a self-evident fact. Addition to or subtraction from this available amount alters the fate of the patient after occlusion.

Amount of Blood Necessary to Preserve Life: Experiments by my associate, David S. Leighninger, showed that when the descending ramus of the left coronary artery was ligated in one step at its origin, 300 cc. per hour to the ischemic area were necessary to preserve the heartbeat. When the circumflex ramus was ligated, 390 cc. per hour to the ischemic area were necessary to preserve the heartbeat. These quantities do not protect against the formation of an infarct. They make it possible for the heart to keep on beating.

The Mautz-Gregg Backflow:[21] This important method of measurement is carried out by placing a ligature on either the circumflex or descending ramus of the left coronary artery, then severing the artery distal to the ligature and determining the amount of blood that flows from the cut end. This blood comes from the intact arteries. In normal dogs the amount varies from several drops per minute to 8 or 9 cc. per minute but in two dogs 17 and 21 cc. were obtained. These dogs with high backflows have a

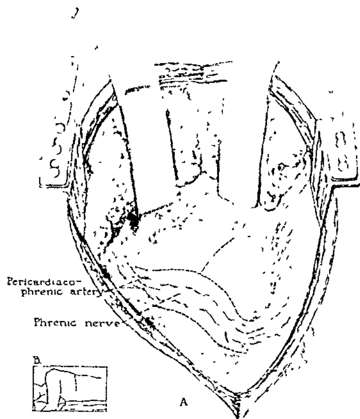


FIGURE 10 Left side of chest is opened by incision between the fifth and sixth ribs as indicated in the inset The pericardial incisions are indicated by the broken lines

good functioning set of intercoronary channels. They were born with them and these dogs would survive descending or circumflex artery ligation. They may be regarded as protected hearts. Nine per cent of normal human hearts have a good set of intercoronaries. They also were born with them. These are the humans who survive an occlusion and if the disease is not too severe after the occlusion they make a splendid recovery. It is desirable to give the ninety-one per cent of the people an equally good

set of intercoronaries so that they also will have a better chance to survive arterial occlusion. The average backflow in dogs is 3.8 cc. per minute or 228 cc. per hour.

Operation: The various steps in the operation are illustrated in Figs. 10, 11, 12, 13, 14, 15. The patient is placed on his right side with the left side up. An incision is made between the fifth and sixth ribs from the sternum laterally for about 20 cm. A self retaining retractor is placed and



FIGURE 11 Placing a suture around the coronary sinus; *B*, needle penetrating the left atrium in a direction parallel and close to the sinus Needle is then turned in a clockwise direction ninety degrees to emerge just superior to the sinus Temporary traction sutures are in the fat to expose sinus

the ribs are spread apart for 10 cm. The pericardium is opened on each side of the phrenic nerve and the lining of the pericardium is thoroughly abraded. The heart is carefully explored for infarct, arterial disease, reduction of pulsation, aneurysm, and enlargement of the heart. A needle with a piece of silk is passed around the coronary sinus 1 or 2 cm. from its stoma in the auricle. The surface of the heart is carefully abraded. A probe 3 mm. in diameter is placed on the sinus and the silk is tied on this probe. The probe is then removed and this narrows the sinus to about the size of

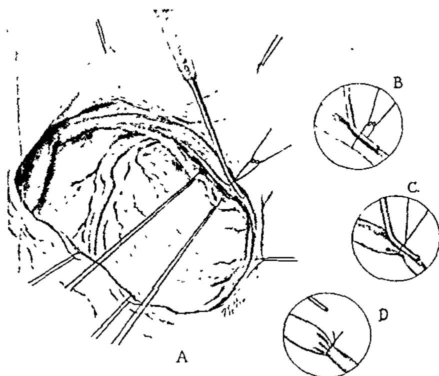


FIGURE 12 Partial ligation of the coronary sinus The ligature is tied on a stilet 3 mm in diameter, as in *A*, *B*, and *C*, and the stilet is removed after the ligature is tied, as in *D*

the probe. Three-tenths grams of powdered asbestos are placed on the surface of the heart. The pericardium is loosely closed. The pericardial fat with its independent blood supply is spread over the surface of the heart as a graft. Sometimes, but not often, anastomoses develop between the fat and the heart. A drainage tube is placed in the chest. Two sutures are placed around the ribs and the soft parts are closed with silk.

What Does This Operation Accomplish When Applied to Normal Dog Hearts? When the descending ramus of the left coronary artery is ligated

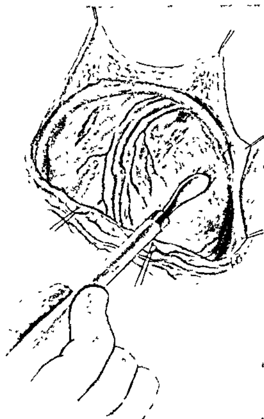


FIGURE 13 Epicardium removed by special burs. Necrotizing chemicals should not be used for this purpose

at its origin in one step in normal dogs the mortality is seventy per cent When this operation was performed on the normal dog and then at some subsequent time this same test artery was ligated the mortality was twenty-six per cent. The mortality was reduced forty-four per cent because of the operation. Likewise the size of the infarct in the dogs that survived ligation was reduced by sixty to seventy per cent because of the operation. The electrocardiogram showed fewer abnormalities because of the operation. The Mautz-Gregg backflow was increased from an average of 228 cc. per hour in normal dogs to an average of 510 cc. per hour in the operated

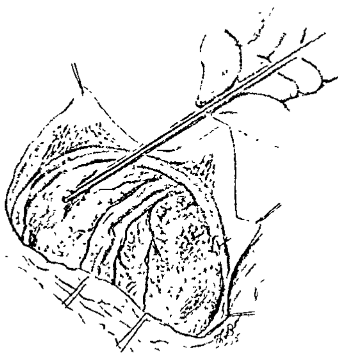


FIGURE 14 Sprinkling of an inflammatory agent (0 2 to 0.3 Gm of coarsely ground asbestos) over the entire surface of heart

dogs. This is an increase of 282 cc. per hour produced by operation. In other words, the operation made available the equivalent of a transfusion of 282 cc. of additional blood per hour to the ischemic area of myocardium when the circumflex artery was occluded and this blood was available at the time of the occlusion. It was made available by the presence of intercoronary arterial channels (Fig. 16).

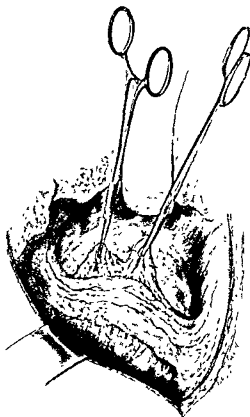


FIGURE 15 Pericardium partially closed Mediastinal fat is used to cover the heart as much as possible Here it is brought beneath the bridge of pericardium containing the pericardiacophrenic artery and vein. In most instances it is attached to the right border of this bridge of tissue

Selection of Patients: Three groups of patients are acceptable for operation. The first group includes those patients who need the operation as a prophylaxis against coronary occlusion in the future. So far no patient in this group has been operated upon but recently a patient, age forty-one, requested advice. His father and two uncles died at an early age from coronary artery occlusion. He wanted to know whether he should have the operation because of his family history. My advice was he should have the operation done now at a time when the risk was minimal or absent and should occlusion develop later on he would be in the group of ninety-one per cent of the humans who are born with a protective set of intercoronary arteries. The second group of acceptable patients includes those who have

had coronary insufficiency without an infarct. Operation should be done in this group when diagnosis of coronary insufficiency is made. The third group includes those patients who have had one or more infarcts. Six months should elapse between the infarct and operation.

Certain patients are not candidates for operation. These include patients with extensive disease, enlargment of the heart, and signs of myocardial failure. Patients who are having progressive symptoms should be given a period of time for the disease to become quiescent before the operation is

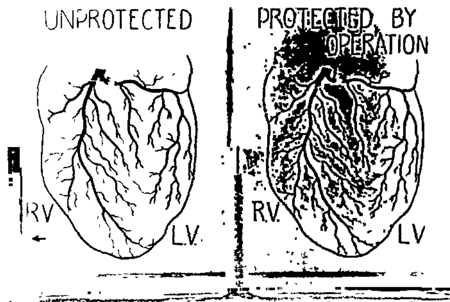


FIGURE 16 The average backflow from the circumflex artery in seventy normal hearts was 228 cc per hour The average backflow in forty-one hearts after operation had been done was 510 cc. per hour Operation added 282 cc per hour This is equivalent to a transfusion of life saving blood to the ischemic muscle This blood is available at the crisis of an occlusion and helps the heart to meet this crisis Medical measures do not add a single drop of blood to *ischemic muscle*

done. If there is any question concerning the acceptability of a patient at any given time, decision for delaying the operation is made and the patient is re-evaluated later. If the blood pressure should fall to 80 mm. Hg under anesthesia before the incision is made and if the blood pressure does not rise to about 100 mm. Hg after waiting one-half hour, the operation is cancelled and is not done at a later date.

Limitations of Medical and Surgical Treatment: Neither form of treatment cures coronary artery disease. Neither stops the narrowing process in the arteries. Neither restores degenerated myocardium. The operation is not a guarantee that the patient will not get a fatal occlusion later on. What the operation does accomplish is to change the coronary circulation so that when an occlusion occurs the heart is more likely to tolerate the occlusion than it would without operation. It should be understood and accepted that a patient can be improved after operation so that he can do

a full day's work. One of my patients worked for nine months; then his pain and disability recurred and he died three months later. This patient died not because the operation did not help him because it did help him for nine months. He died because his disease got worse and coronary inflow was reduced to levels not compatible with life. Scientific evaluation requires a reasonable attitude towards this disease.

Results of Operation: This operation was applied to 170 patients with coronary artery disease in a period from January, 1951 to January, 1956. Some of the patients accepted during this period had enlargement of the heart and were regarded as salvage cases. The operative mortality was two patients. The early postoperative mortality was nine patients, making a total of eleven patients or 6.5 per cent. A long term follow-up study was made on 137 patients who had gone six months to five years after operation. The average follow-up period was two years. Eighteen out of this group died, which was 13.1 per cent. We do not have a strictly comparable group of nonoperated patients for comparison. Lindgren reported a series which probably most closely resembles ours and the mortality in this nonoperated group in two years was thirty per cent. We believe that the operation protects the human heart in the same way it does the dog heart. Human specimens show intercoronary vessels and it is reasonable to expect this operation to be a life saving procedure for patients who have coronary artery occlusion.

The clinical results in 100 patients who have gone from six months to five years after operation are favorable. Forty per cent of these patients state that they have no pain whatsoever and forty-eight per cent state that they have less pain than before operation. This is a total of eighty-eight per cent who have had relief from pain. The results were analyzed from the standpoint of their ability to work. Thirty-four per cent stated that they were better able to work and had no limitations. Fifty-six per cent stated that they were better able to work than before operation but that they did have some moderate limitation of activity. From the standpoint of being able to work ninety per cent showed improvement. Some medical cardiologists believe that these favorable results are based on the mental reaction of the patient toward the operation rather than any favorable changes which were produced in the coronary circulation. In view of the scientific measurements, upon which this operation is based, this attitude is scarcely less than nihilistic. Most of the patients state that the tightness in their chest leaves them as early as three or four days after operation. Most of the patients say their pain is better before they leave the hospital. Occasionally the patient does not experience improvement for three or four months after operation. Never had we had the experience of a patient condemning the operation as not having helped him and in our best patients the results are almost unbelievably good. As of May 29, 1956 the last sixty consecutive patients were operated upon and the mortality was 0.

Other Operations for Coronary Artery Disease: Other surgeons have worked on this subject and operations have been developed which bear the names of Thompson,[22] Vineberg,[23] and Fauteux.[24] Thompson used talcum

powder applied to the surface of the heart as an inflammatory agent. He has operated on a fairly large number of patients and results have been good. Vineberg has used the internal mammary artery as a graft to the left ventricle. This artery is dissected free; it is ligated and cut but one or more of the small branches to the intercostals are left open. This naked artery is then pulled into a tunnel into the wall of the left ventricle. Arterial communications develop by a process referred to as "budding." Both of these operations have been tested in the writer's laboratory and it was found that the Vineberg operation is beneficial on the basis of production of intercoronary channels by the trauma of the operation. The Thompson operation was also beneficial on the same basis of the intercoronary channels. Neither of these procedures in our hands produced as much protection as the operation described by the writer. The Fauteux operation consisted of ligation of the magna cordis vein and removal of nerves at the base of the aorta.

RESUSCITATION[25]

Introduction: When the heart stops beating and "death's at hand" ventricular asystole or ventricular fibrillation replace the heartbeat. The factor producing death is not always known. Sometimes a series of conditions lead up to it. A drug used in anesthesia may be the cause, a reflex, anoxia, accumulation of carbon dioxide, manipulation of the heart, blood loss, position of the patient on the operation table, intrinsic disease in the heart, and other conditions may be the cause of death. Sometimes the accumulation of electricity in the heart may destroy the coordinated mechanism and produce fibrillation. Often the death factor is small, reversible and preventable. In view of these facts prevention of cardiac arrest and the resuscitation procedure are of great importance in saving life and they should be included in the training courses in medicine both in the undergraduate and postgraduate levels. The surgeon and the anesthetist must necessarily be able to apply the procedure. Society regards this knowledge as a requirement of the medical profession. Courses in resuscitation are given in various parts of the country.

Who Can Be Resuscitated? It is difficult to draw a line between those who can be resuscitated and those who cannot be resuscitated. Several general statements may be made. If success is not possible then the procedure should not be attempted. In this group in which it should not be done are the patients who have been dead for over six minutes, patients who have incurable disease including cancer, malignant gliomas, severe disease in the heart, and other conditions. In the group in which it should be done are the patients with a good heart and a good pair of lungs, patients who are having tonsils removed, a hernia repaired, teeth extracted, and many other medical or surgical procedures. Resuscitation has been extended to patients who had fatal heart attacks from coronary artery disease. Two successful cases have been reported and a new door to medical progress has been opened by these successful cases. Most victims of coronary artery disease do not die of reversible damage in the heart; they die of electrical currents in the heart and these can be dissipated by pump-

ing the heart by hand. In some of these patients the death factor is a small factor similar to stopping and starting the pendulum of a clock, or turning on or off the ignition switch of a motor car. Sometimes the only thing the heart needs is a second chance to beat.

Necessary Apparatus and Supplies: These include a knife to open the chest and a tube to inflate the lungs. Later on a self retaining retractor relieves pressure on the wrist of the hand pumping the heart. A properly fitting intratracheal tube with an inflatable cuff and a bag of oxygen are desirable. A shocking device is necessary when the heart is fibrillating. Anesthetic agents are sometimes needed and clamps and ligatures to close the chest are needed.

The essential items should be at the head-end of every patient who is operated upon, whether the anesthetic be general or local. This should be a rule laid down in every hospital. These items are an intratracheal tube, a laryngoscope, a rubber bag, and a tank of oxygen.

Can Resuscitation Be Extended Beyond the Hospital? This is, indeed, possible if the necessary personnel and equipment are available. The people who die on the golf course, at an athletic contest, watching television, and so on are good candidates for resuscitation because they die of electric currents in the heart. These currents are produced by oxygen differentials in the heart muscle. One area has a higher oxygen content than an adjacent area and currents are produced. These currents are not related to infarction of muscle; they may form without infarction and the heart may be a good organ capable of beating for years.

Success has spread from the operating room to the other parts of the hospital. In the University Hospitals of Cleveland a successful procedure was started on a medical ward and completed in the operating room Another patient dressed in his street clothes, about to leave the hospital after getting an electrocardiogram, fell over dead from a heart attack. He was saved. This patient is practicing medicine nine months later.

Extension of the procedure to society at large involves several problems, which can only be mentioned. One is the training of nonmedical personnel to open the chest and pump the heart. Another problem is to provide resuscitation kits which contained all necessary supplies and these kits could be serviced at regular intervals. Another problem is acceptance by society. Perhaps medicolegal problems would arise. No doubt lives could be saved by this development.

The Resuscitation Procedure

It should be divided into two parts. Failure to break it down into these parts leads to confusion and failure.

Part One: This consists of restoration of the oxygen system. Nothing else matters when the oxygen system has stopped except starting it again. It is started by introducing oxygen into the lungs and then circulating the oxygen to the brain. The best way to get oxygen into the lungs is to insert an intratracheal tube, connect the tube to a bag of oxygen and squeeze the bag. The best way to circulate it to the brain is to pump the heart by hand. The chest must be opened wide enough to get your hand on the

heart; then the heart is emptied. The crisis is over when these two things have been accomplished. The brain cells degenerate in three to five minutes without oxygen and this time limitation can determine success or failure. These precious moments should not be wasted; one should not "monkey around" and this is more than a figure of speech.

Part Two: This consists in restoration of the heartbeat. The emergency action is over but circulation of oxygen must be continued with nothing longer than momentary interruption at any one time. As a rule the heartbeat is easily restored. A few squeezes of the heart often starts it beating. If it does not start right away the pericardium is opened and the heart is observed. An electrocardiogram may be taken. If asystole is present 4 cc. of 1 to 10,000 epinephrine solution is injected into the cavity of the right ventricle. If fibrillation is present the heart is shocked using larger electrodes on each side of the heart, and about 1.5 amperes of current. Sometimes fibrillation recurs in which event repeated shocks are necessary. Sometimes 2 to 4 cc. of one per cent procaine solution injected into the cavity of the right ventricle will aid in stopping the fibrillation. Then epinephrine and massage are used and the heart will start beating. When dealing with a good heart in a patient whose brain has not died one should continue with his effort at resuscitation for several hours if necessary. Any good heart can be made to beat again.

Recommendation: Special training in resuscitation should be a requirement for the practice of surgery and anesthesia. In the absence of training it is recommended that one of the special courses be taken.

OPERATIONS ON CARDIAC VALVES

In the first edition of this work, 1940, the following statement was made: Ten attempts on the mitral valve were carried out—seven by Cutler,[26] one by Allen and Graham,[27] one by Souttar,[28] and one by Pribram.[29] Doyen inserted a knife into the right ventricle for the purpose of cutting a stenosis of the pulmonary valve. The patient died a few hours after the operation and at necropsy there was found a congenital narrowing of the conus arteriosus and perforation of the interventricular septum. Griffin tried to dilate a stenotic aortic valve by inserting a finger through the invaginated wall of the aorta.

The writer spent two years in the experimental laboratory working on the mitral valve under Cutler and assisted him in operation on patients. The human hearts that we studied were preserved in formalin; the valve leaflets were either like shoe leather or calcified and it looked as though a piece would have to be excised from the valve in order to reduce the stenosis. This in turn created insufficiency. Not a single specimen was examined in which the leaflets were soft and the commissures could be broken open. It is possible that later on the sulfa drugs and the antibiotics have made the pathology of the valve more amenable to surgical correction. The ventricular approach was used. The chest was opened by splitting the sternum longitudinally. The operating room dripped with drama. It required great spirit to do these operations, and Cutler's name deserves a place in the development of heart surgery even though this work

did not establish this operation as an acceptable and beneficial procedure (Fig. 17). In 1946 new interest developed in this subject and the names of Bailey, Smithy, Brock, and Harken are associated with the development of the operation for mitral stenosis as we know it at the present time.[30]

Mitral Stenosis

Selection of Patients: How much incapacity is necessary in order to recommend surgical operation? Is the diagnosis of the disease enough for operation? In general the attitude is towards early operation especially if



FIGURE 17. Elliot C. Cutler (1888-1947). For his sustained and long-term effort in the surgical research laboratory working on the heart and for his early attempts to operate on the mitral valve

the x-ray shows left auricular enlargement and if there are early signs of fatigue and dyspnea on exertion. Auricular fibrillation is an added indication for operation because of the possibility of emboli. Rheumatic activity should be treated intensively and operation should not be done until this subsides. Only occasionally is the operation done under twenty years of age. There is almost no limitation to the operation because of the seriousness of the illness. Patients with severe failure and weight loss have been accepted for operation. Mitral regurgitation is not a contraindication to operation. An important problem is to decide whether stenosis is present with the regurgitation. In some of these cases exploration is indicated and it is determined at operation whether there is any stenosis that can be

relieved by operation. It is readily possible to pass up some of these severely crippled patients who could be helped by operation In patients in whom the decision for operation is difficult, the following conditions favor operation—right ventricular hypertrophy, high pulmonary artery pressure, the absence of marked left ventricular hypertrophy, and a diastolic murmur.

Operation: The approach is usually through the left side between the fourth and fifth ribs. A purse-string is placed around the base of the left auricular appendage. A non-crushing clamp is placed on the base of the appendage and the appendage is opened. The right index finger is introduced through the appendage. The finger feels for regurgitation, the anatomy of the valve leaflets, the presence of calcium in the leaflets, the condition of the two commissures, the size of the mitral orifice and the cordae tendinae. If there are any clots adherent to the auricular wall these are not dislodged. The valve is opened in the commissures. Special knives are used but in the majority of patients the commissures can be torn open by the finger. The finger is then withdrawn and umbilical tape is wrapped around the terminal phalanx, another glove is placed on the hand so that the tape is covered and the valve is opened in stages up to a measured diameter of 2.5 cm. or larger. If the commissures cannot be torn open in this way the commissures are cut. When a cut is made it is not always possible to avoid creating some regurgitation The appendage is ligated at its base, it is amputated and the base is sutured.

Complications: The most important complication is the dislodgement of a clot in the auricle or breaking off a piece of calcium which is carried to the brain. If the appendage contains clots these can be removed and free clots can be flushed out of the appendage. If the auricular wall and the appendage harbor an extensive clot it is advisable to select an area where there are no clots for the approach. This can readily be done. Dislodged clots have been removed from the carotid arteries, the aorta and the vessels of extremities after operation on the valve. Sometimes the rheumatic infection flares up immediately after operation or weeks or months later Because of this possibility prophylactic penicillin or sulfa drugs are given for several months after the operation.

Results: The clinical results after operation are excellent as a rule. If the patient has a tight stenosis and some of them are as small as 6 mm. in diameter and if the valve is soft and readily opened the results are indeed excellent. These may be regarded as cures There are various degrees of improvement ranging from none to good. Some of the valves are heavily calcified and after the valve is opened it still stands out in a transverse direction and does not allow free flow of blood. Another factor that may impair the result is the presence of regurgitation. The myocardium is sometimes the seat of rheumatic infection and its capacity to function may be impaired. The risk of the operation in the best type of patient is almost zero. In patients with extensive disease, with accompanying regurgitation, with calcified valve, with extreme enlargement of the heart, with the presence of clots, with emaciation (and some may weight only 36.3 to 40.9 kg [80 to 90 lb.]) then the risk of operation is high When such a patient

is operated upon it is a calculated risk that is being taken and sometimes it is advisable to accept the risk because occasionally considerable help can be given by operation, sometimes more than was anticipated.

Mitral Insufficiency

This is a very common lesion and surgeons have been trying to devise operation whereby the regurgitation can be reduced. So far this effort has



FIGURE 18 John Gibbon, Jr. (1903-). For his original work on open heart surgery.

not been altogether unrewarding. There are some successful cases where the valve ring was narrowed by sutures but by and large this development remains for the future. It is indeed difficult or impossible to place sutures using the closed method, *i. e.*, where you cannot see inside to place the sutures. Open heart surgery would be an important aid for doing plastic operations on the valves.

Aortic Stenosis

This lesion can be torn or cut open with improvement in the circulation. It is not nearly as amenable to surgical correction as the mitral valve because the deposition of calcium in the aortic valve may be very heavy and the danger of the operation is considerably greater. There are two

approaches to the valve. One is through the left ventricle. A dilator is introduced through the wall of the ventricle and into the orifice of the aortic valve. There are instances in which the orifice is so small and the plane of the valve is so tilted that even at autopsy it is not possible to enter it. As a rule the orifice is entered and the calcified tissue is cracked open. Some of these valves are so calcified that they cannot function as valves. There is danger of fibrillating the heart by touching the septum. There is also a problem of hemorrhage from the wall of the ventricle.

The other approach is through the aorta. The aorta is pinched off with a Beck or Potts clamp. The aorta is opened and a sleeve of nylon is sutured to the aorta. This allows entrance and exit to the valve. Time can be taken to find the aortic orifice without making a false passage. The valve is then cracked open. The sleeve is removed and the aorta is sutured.

The operation can produce good results. The mortality ranges from about ten per cent in the most favorable cases to twenty per cent or higher in patients with severe failure. In these patients a calculated risk is taken when the prognosis without operation is a matter of a few months of life.

Aortic Insufficiency

Hufnagel devised a plastic valve which contains a ball and which allows blood to go in one direction. This valve is in several sizes. It is placed in the aorta, just beyond the descending part of the arch. It is indeed remarkable that this valve can remain in situ after it has been placed. In this position the valve prevents backflow beyond the valve It does not prevent backflow from arms and head. Patients have been improved by this operation. The risk is high in patients with advanced disease. Some surgeons who have done the operation do not recommend it in their hands and refer the patient to Hufnagel for him to do the operation.[31]

ATRIAL SEPTAL DEFECTS

There are several types of defects in the auricular septum referred to as absent septum, ostium primum, ostium secundum and atrioventricularis communis. These defects are developmental. Diagnosis is established by catheterization of the heart. Operation is indicated in those patients who have progressive symptoms, mild pulmonary hypertension, early cardiac failure and those in whom there is a large shunt. The operation should be done before severe pulmonary hypertension develops. The operation is not recommended in patients with no symptoms and small shunts. For the correction of these defects some surgeons have opened the heart and sutured the defect under vision Others have employed various procedures which do not envolve open heart surgery. One of these methods consists of using a finger in the right atrial appendage as a guide to placing sutures between the rim of the defect and the atrial wall. A series of sutures brings the atrial wall and the defect together so that it is closed. In doing this operation care is taken not to occlude partially either vena cava. Another method consists of placing a suture on a large slightly curved needle so that the septum is puckered together when the suture is tied. The suture is passed in the atrial wall close to the aorta but not in the

aorta. The needle is guided by a finger in the auricle. The needle penetrates the septal wall around the defect and emerges superior to the coronary sinus. Some defects can be readily closed in this manner. When the defect extends down into the interventricular septal area it is not possible to close the defect. Open heart approach will probably make some of these operations successful. The prognosis in patients with severe pulmonary hypertension is grave and this is a contraindication to operation. The risk of operation is about ten per cent mortality. Closure of the defect can produce complete cure.

INTERVENTRICULAR SEPTAL DEFECT

These have been closed by open and closed methods but the technic has not advanced to the stage where operation is recommended. After open heart surgery has been made safer these defects probably will be closed successfully without a high mortality. At present operation is not recommended for this lesion.

OPEN HEART SURGERY

The original idea of open heart surgery was conceived and studied by Dr. John Gibbon Jr. of Philadelphia. He spent many years working on this subject during a period when no one else was interested. He has made a monumental contribution to surgery. In the past decade many surgeons have become interested in this development. Many methods have appeared. There are now many different oxygenators, pumps, defoaming devices, etc., all aimed at making it possible to open the heart. Venous blood is removed from the venae cavae; it is oxygenated and then returned to an artery. The heart is then opened and corrective operation carried out. Then the various tubes are removed. There are many problems in this work and these can scarcely be discussed in this chapter. Progress is being made and no doubt positive steps will be accomplished out of a large amount of effort now being made. Greater success is just around the corner so to speak. This is the credo of the scientist and it keeps him trying to do things better. The heart has been opened under conditions of hypothermia and this method has been more successful.[32] It is scarcely necessary to comment upon the possibilities of open heart surgery. One of the most pressing is the repair of mitral insufficiency.

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ROBERT P. GLOVER, M.D.
AND
JULIO C. DAVILA, M.D.

23

Cardiovascular Surgery

Introduction: For centuries the therapeutic problems of heart disease whether vascular, valvular, or myocardial were considered to be almost entirely within the province of the internist. With the demonstration that the heart and great vessels could be manipulated, clamped, and invaded with safety and dispatch provided certain basic principles were heeded, an entirely new concept of cardiac anatomy, pathology, and physiology has emerged. *As a result, the past decade has witnessed the development of* cardiac surgery assume a position of major importance, to climax a half century of far-reaching surgical achievement. This does not imply that surgeons of the present era are of greater skill or bolder in their approach to seemingly impregnable pathologic situations. On the contrary, the reverse may well be true, for it has been the intrepid and fearless courage of many unsung pioneers of the past working in uncharted seas that has paved the way for present day developments.

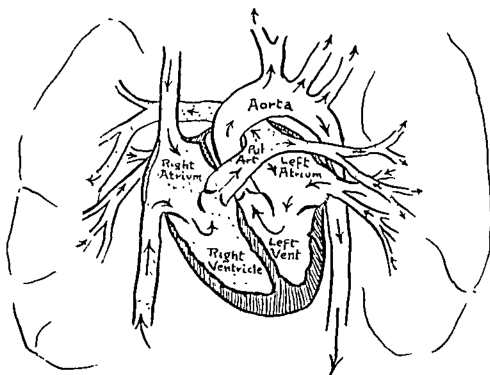
Cardiovascular surgery has not only the very considerable problems of its own inherent anatomic and pathologic distortions with which to contend but also must face and overcome the physiological deterrents presented by its surrounding environment, the thorax. Thus, the evolution of this surgery has been the natural development of thoracic medicine and surgery itself in all its aspects—laboratory, experimental, and clinical—and it is, therefore, impossible to point out any one cornerstone or pillar upon which the vast structure of such a pyramiding new enterprise rests.

Developmental Considerations: Of primary importance in its development, however, are these basic contributions: (1) The knowledge of the embryologic and anatomic development of the heart and its adjacent vascular structures as they occur normally and wherein they deviate into the many congenital malformations, many of which are now recognizable clinically. (2) The accumulation of pathologic data pertaining to the type and forms of distortion left in the wake of certain acquired disease entities such as rheumatic fever, syphilis, arteriosclerosis, traumatic injuries, acute infections, and the like. (3) The heart, being as it is a pump, carries out its work according to established mechanical and physiological principles. Normal measurements of this activity have been recorded by the physiologist for years. Any deviation due to defects within the pump itself or its vascular attachments likewise are measurable, and such physiologic data in health and disease are of paramount importance in the proper appreciation of the surgical problem at hand (4) Improvements in anesthetic meth-

ods and the development of controlled respiration (positive pressure) within the open thorax have overcome the hazards of the collapsed lung so that thoracic and, of course, cardiovascular surgery can now be carried out with the same measure of confidence enjoyed in other branches of surgery not confronted by this problem. (5) Again, as in surgery as a whole, the availability and proper use of blood transfusions to combat shock and antibiotics to prevent infection, both intravascular and within the pleural and pericardial spaces, have supplied a great measure of safety unknown in years gone by.

Anatomical and Physiological Considerations in General: The heart is a hollow, muscular pump containing four separate and distinct chambers separated by muscular septae and thin, pliable valves. The blood, having traversed the body, returns to the right atrium through the superior and inferior venae cavae. It then passes through the tricuspid valve into the right ventricle, through the pulmonary valve and main pulmonary artery which divides, sending branches to the two lungs. The pulmonary artery, although called an artery, carries venous or unoxygenated blood. The blood returns to the left atrium *via* the pulmonary veins which conversely carry arterial or oxygenated blood, although called veins. From left atrium the circulation passes through the mitral valve into the left ven-

TO HEAD AND UPPER EXTREMITIES



TO TRUNK AND LOWER EXTREMITIES

FIGURE 1. Diagrammatic representation of normal circulation

tricle and out into the aorta through the aortic valve. Having traversed the entire body the blood again enters the right heart to endlessly repeat the cycle (Fig. 1).

Thus, the heart and peripheral circulation is a completely closed system and as such is affected or responds according to the established principles of fluid circulating in a confined and isolated circuit. No major or even minor defect (such as an obstruction, leak, cross communication, etc.) anywhere in the heart or circulation can exist without eventually exerting a profound effect upon the entire system, both locally and as a whole. For example, a peripheral arterio-venous fistula will show the local effects of inadequate circulation of the affected extremity and within time the heart itself will enlarge and decompensate because of the additional circulatory strain. Similarly, the pulmonary circulation and the right heart will evince failure secondary to obstruction within the left heart, such as in mitral stenosis, so that one can never consider a cardiovascular problem as affecting one isolated area alone.

The heart is actually two hearts beating simultaneously, each consisting of two chambers and two valves and separated from its fellow by an intact *atrioventricular septum. Normally, there can be no intermingling of* blood between the two hearts save by passage of the blood from the right side through the lungs and into the left heart. In effect, therefore, the heart surrounds the lungs. It is natural under these circumstances that the first subjective indication of heart disease is frequently pulmonary (dyspnea, hemoptysis, etc.) for the lungs reflect the mechanical integrity of the vascular pump.

The right heart is thinly muscled. The vascular pressures within it are low. It needs only to propel the vascular stream into the equally low pressure pulmonary vascular bed and has no need for the development of high heads of pressure The left heart with its attached aorta, on the other hand, must maintain high pressure levels within itself and throughout the body, and it even supplies the impetus for the circulating blood to return to the thorax through its venous extensions For this reason, it is a heavily muscled structure capable of great effort under normal conditions and even greater under abnormal circumstances. In consequence, should there be an abnormal opening (congenital or otherwise) between the two hearts or their circulations, the shunting flow of blood will be from left to right, from high pressure to low pressure. Only under extreme circumstances can right-sided pressures equal or surpass left heart pressures with a resulting right to left shunt (advanced mitral stenosis, combinations of congenital defects, as in the tetralogy of Fallot, etc.) described below in the text.

The valves of the heart—four in number—are normally thin, pliable, cellophane-like structures. They are passive in nature and in themselves cannot actively contract. They open and close only in response to pressure changes on their two sides and thus can be buffeted about by the cardiac myocardium at will. They are designed, as are valves in all mechanical pumps, to keep fluid moving in one direction only—forward. The tricuspid on the right and the mitral valve on the left perform the heaviest

duty, as they each lie between two constantly contracting muscular chambers. For this reason, their cusp margins are reinforced by a system of guy wires (chordae tendineae) attached to papillary muscular extensions from the ventricular myocardium and contract with it, thus drawing the chordae tendineae taut to prevent eversion of the valve cusps into the atria as they close during ventricular systole. The pulmonary and aortic valves lie within the orifices of their respective vessels, terminating the outflow tracts of the right and left ventricles. Each consists of three sail-like cusps attached

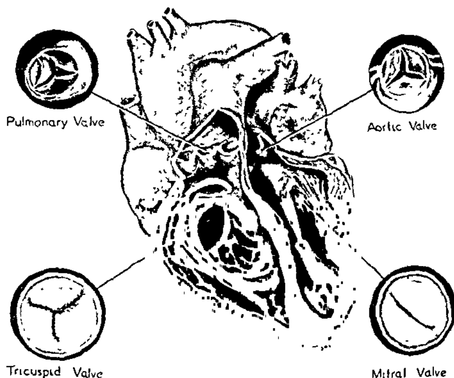


FIGURE 2. Anatomical dissection of the heart to show the position and structure of the cardiac valves

and cupped in such a way as to flatten against the vascular wall during systolic ejection and approximate perfectly along their cusp margins during ventricular diastole. The cusps of the aortic valve are somewhat thicker and stronger than those of the pulmonary valve for they must cope with greater intracardiac and vascular pressures The aortic valve is further complicated from a surgical reconstructive point of view by the presence of the coronary artery orifices lying immediately distal to the valvular attachments and thus, they too, may become affected by any pathologic change within the valve itself (Fig. 2).

Three of the four valves are readily accessible to surgical exploration. The tricuspid and mitral valves can be reached routinely by the exploring index finger of the surgeon through the auricular appendage without interfering appreciably with intracardiac circulation. The pulmonary valve lies superficially within the exposed pulmonary artery, extending from the

superior-anterior aspect of the right ventricle, and can be palpated either through the intact pulmonary arterial wall or by introducing the finger through a small incision in the outflow tract of the right ventricle. The aortic valve, on the other hand, is the most inaccessible, for it lies deep within the cardiac mass. Although it can be reached through the wall of the aorta, it is best and most safely approached by using probe-like instruments introduced through the left ventricular myocardium near its apex. Such instruments are guided upward into the valve by following the course of the interventricular septum (described below in the text).

In general, it may be stated that most of the pathologic conditions with which the surgeon must deal in the right heart are congenital in nature, whereas, those in the left heart are acquired. This refers primarily to valvular distortion, to be sure, but such a dictum can be used as a rough axiomatic rule. Defects within the interatrial or interventricular septum, congenital in nature, are strictly speaking, neither right nor left but the surgical approach is usually from the right side.

Diagnostic Considerations: In every subdivision of medicine and surgery there are certain diagnostic methods peculiar to the organ or functional system under suspicion. Although not primarily responsible for the recent renaissance of cardiovascular surgery, nevertheless, angiocardiography and cardiac catheteriatzion have been developing simultaneously with it and already have gone a long way toward a more complete clarification of the more obscure malformations with which the surgeon must be prepared to cope. It is almost axiomatic that the cardiac surgeon must know before surgical intervention the exact diagnosis or location of the offending lesion, for he does not enjoy the latitude of exploration available to the abdominal surgeon. The heart lies between the pleural reflections of the two lungs and, therefore, must be approached, as a rule, from one side or the other. When partially exposed it cannot be handled indiscriminately, dislocated, or turned about in quest of the trouble. The surgeon must depend upon what he sees on external surfaces, palpatory thrills, gentle intracardiac probe, or digital exploration rather than gross manipulation, lest serious and fatal cardiac arrhythmias develop. For these reasons, it is of the utmost importance that whenever possible a pinpoint diagnosis be at hand so that definitive surgery can be directed immediately to the pathology and corrective procedures carried out with dispatch

Angiocardiography is a method of cardiovascular visualization in which an opaque, inert substance (diodrast seventy per cent is commonly used) is injected into the venous circulation in sufficient quantity and concentration to outline that portion of the vascular bed under suspicion. When used for examination of the heart and great vessels, the course of diodrast, as it passes through the cardiac chambers from right to left, is followed by a roentgenographic device capable of taking a rapid succession of films (one to two per second) which can then be examined for the suspected malformation. This type of study is particularly adapted to the detection of lesions within the right heart and pulmonary artery, although in small children it may be quite adequate to outline the cardiac chambers on the left, as well as, the aorta (Fig. 3). In larger children and adults it is often

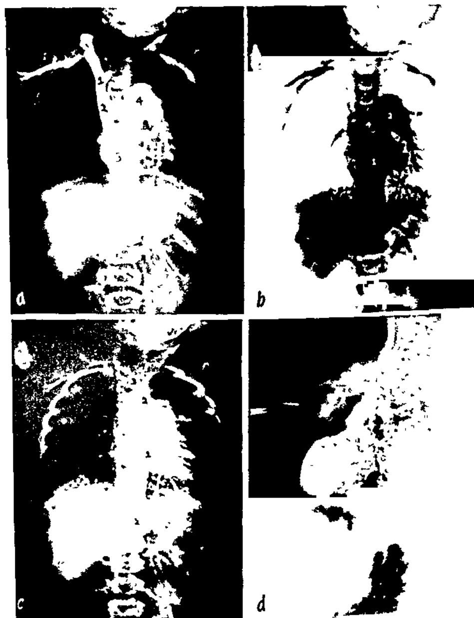


FIGURE 3 Angiocardiogram of the normal heart and great vessels A, Diodrast outlining the superior vena cava (1 & 2), right atrium (3) and outflow tract of right ventricle, and main pulmonary artery (4) at its bifurcation B, Right ventricle (1), main pulmonary artery (2), branches of left pulmonary arterial bed (3) and right main pulmonary artery (4). C, Left ventricular outflow tract (1), the aorta at its arch and shown within the upper abdomen (2), innominate artery (3), carotid arteries (4), right subclavian artery (5). D, Lateral angiogram showing the complete sweep of the thoracic and abdominal aorta

of greater value, when lesions of the aorta are suspected, to introduce the dye directly into the aorta where its high concentration supplies more adequate visualization. This is necessary, because dye passing from the right to left heart must traverse the tremendous pulmonary vascular bed where it may become so diluted in the total blood volume as to render it useless as a visual aid when it reaches the left side. Thus, direct aortog-

raphy for delineation of aortic anomalies, congenital and acquired, has also become a standardized procedure whenever its use seems essential.

Cardiac catheterization, when properly performed and intelligently interpreted, is an even greater aid to intracardiac diagnosis than angiocardiography. By exposing a small vein in the antecubital fossa of either arm, or if necessary, using the saphenous vein in the upper thigh, a long, pliable catheter of small caliber can be introduced into the major veins of the extremity, passed on into the vena cava (superior or inferior), thence into the right atrium, through the tricuspid valve and into the right ventricle. By gently manipulating the exposed end of the catheter, its intracardiac tip can be guided into the outflow tract of the right ventricle,

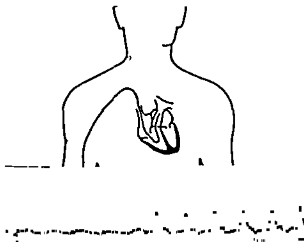


FIGURE 4. Diagrammatic representation of cardiac catheterization showing the catheter passing up the right basilic vein, down the superior vena cava into the right atrium, through the tricuspid valve, right ventricle, and pulmonary valve and lying in the main pulmonary artery It can be passed on into either right or left pulmonary artery Pressure tracings as shown below from the right ventricle and pulmonary artery

through the pulmonary valve into the pulmonary artery and out into either of its right or left branches, as far as the size of the vessel will permit. For obvious reasons it cannot be passed on into the left heart, although considerable information concerning the left atrium and ventricle can be obtained indirectly without actually entering those chambers (Figs 4 & 5).

The information derived from this study is primarily of three types, and when correlated with the clinical symptoms and findings, will often lead to an exact diagnosis which, heretofore, could only be suspected but not proved.

(1) As the catheter is opaque its course during introduction may be followed fluoroscopically. Should it take a course obviously contrary to normal pathways, such as entering the left atrium from the right through an interauricular septal defect, this deviation can be immediately detected and diagnosis established. Thus, the observable course of the catheter acting as a probe may, upon occasions, provide the necessary information, although its use in this manner is understandably limited

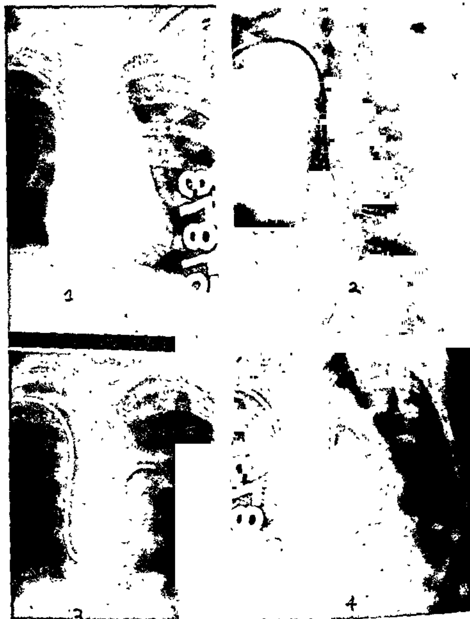


FIGURE 5. Cardiac cathete ... basilic
vein, down the superior ven ... (2),
pulmonary artery (3), and ...

(2) At any point during the passage of the catheter, blood samples may be withdrawn and subjected to laboratory analysis for oxygen content. Such samples are usually withdrawn from the vena cava, at various points within the right atrium and ventricle, as well as, in the pulmonary artery and its branches. As the normal values for oxygen saturation are well known and established in all these areas, any deviation above the normal becomes readily apparent, and direct evidence of an arterial shunt from the left heart between the atria, ventricles, or from aorta to pulmonary artery, can be appreciated. Thus, arteriovenous admixtures of

blood within the right heart, as detected by oxygen content, can herald the presence of intracardiac anomalies at any level, particularly those in *which there is an abnormal opening between the two sides of the heart.*

(3) Similarly, by attaching a manometer to the exposed end of the catheter, pressure readings at any level can be recorded. Again, normal pressure ranges in all the above described areas are known. If the normal pressures have become increased, either in a localized area or throughout the right heart, it denotes a shunt of blood from the high pressure left heart into the low pressure right heart, or of an obstruction (valvular or otherwise) to the normal flow of blood into the pulmonary vascular bed.

It must be clearly understood that angiocardiography and cardiac catheterization are purely diagnostic adjuncts in the overall study of the cardiac patient. There can be no substitution for the clinical appraisal of the experienced cardiologist who must be in attendance, working in complete cooperation with the cardiac surgeon whenever surgical intervention is being considered. His armamentarium, in addition to a thorough physical examination, with stethoscopic evaluation, has long included the electrocardiogram, an estimation of circulation times, venous pressures when indicated, and complete cardiac roentgenography with lateral and oblique exposure, as well as, the standard postero-anterior film. Barium should always be employed to outline the esophagus for the detection of individual chamber enlargement. In recent years, careful and intelligent fluoroscopic examination of the heart, with observance of its total and individual chamber size and action, has taken on great significance and is perhaps as valuable as any other single objective diagnostic aid By the *correlation of all available data the cardiac anomaly or defect can usually* be recognized with a considerable degree of accuracy. Under these conditions the surgeon can resort to his operative intervention with greater assurance and the procedure will be attended by a marked degree of success.

In any new and rapidly developing field of surgical endeavor, it is imperative for the student to have a proper and thorough understanding primarily of those conditions for which the surgeon has developed an established and standardized procedure—one which has proved itself by the passage of time. Toward this end the following outline has been prepared which will provide the basic framework of successful cardiovascular surgery to date. To this, in years to come, will be added many other conditions, both congenital and acquired, for which surgical intervention will be advisable.

Cardiovascular Surgery

A *Congenital*
- I Great Vessels
  - a Patent ductus arteriosus.
  - b Coarctation of the aorta
- II Intracardiac
  - a Pulmonary stenosis.
  - b Tetralogy of Fallot
  - c. Tricuspid atresia

d Septal defects—auricular and ventricular.
e. Transposition of great vessels.

B. Acquired—heart and pericardium.
I. Trauma.
II. Infections.
a. Acute pericarditis.
b. Chronic constrictive pericarditis.
III Rheumatic heart disease—valvular.
a Mitral stenosis
b. Mitral insufficiency.
c. Aortic stenosis.
d. Aortic insufficiency.
IV. Tumors of the heart
V. Coronary artery disease.

C. Cardiac standstill and resuscitation.

D Extracorporeal circulation and corporal hypothermia

A. CONGENITAL

I. Great Vessels

(a) Patent Ductus Arteriosus

Definition: The ductus arteriosus is a vascular communication between the pulmonary artery and the aorta during fetal life. At birth, or shortly thereafter, it normally atrophies to form an obliterated fibrous cord (ligamentum arteriosum). When it fails to involute, and remains an open vessel, it is called a patent ductus arteriosus. Synonym—ductus (Fig. 6).

Pathophysiology: During the period of gestation, the fetus is a completely parasitic structure whose every requirement is supplied through the maternal placenta. The fetal lungs, therefore, do not carry out their normal function of respiration and consequently there is no necessity for the entire circulation to pass through the pulmonary vascular bed. Thus, right heart outflow passes into the main pulmonary artery and much of it, instead of proceeding into the lesser circulation, flows directly through the ductus arteriosus into the aorta. This can occur, for the fetal heart has not developed its eventual gradient of pressure (left higher than right), nor does it do so until after birth. At this stage right and left heart pressures are equal. Essentially then, the lungs are by-passed but the continuity of the circulation is maintained. The first gasp of the newborn child initiates expansion of the lungs and a vast pulmonary vascular bed is opened in its entirety to receive the outflow from the right ventricle. A low-pressure lake of great size is now available to the blood from the right ventricle, hence, taking the course of least resistance, normal pulmonary parenchymal flow is established.

At this point, the ductus arteriosus, being no longer either essential or desirable, begins its obliteration process which may take weeks or months. Many theories have been advanced as to the etiology of this involution but

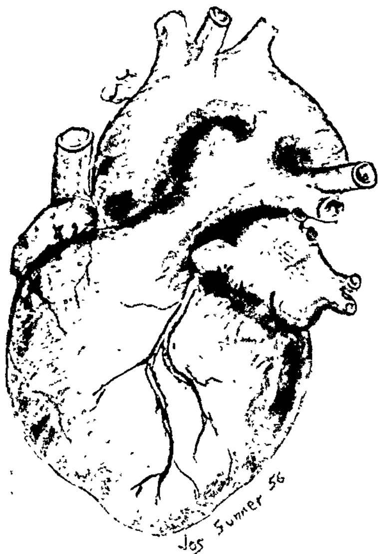
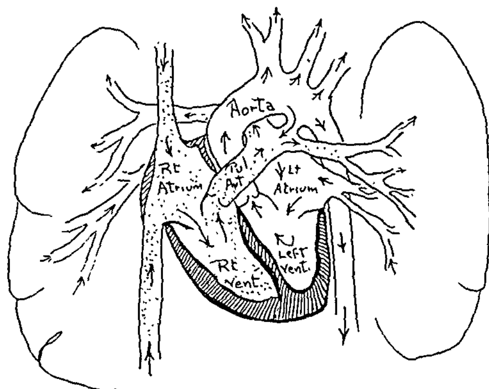


FIGURE 6 Heart and great vessels to show the anatomical location of the patent *ductus arteriosus.*

no actual reason is known other than that the established laws of natural development proceed inexorably despite the incomprehension of man.

In a small percentage of instances, reasons again not known, the ductus does not obliterate and its continued patency brings about a reversed effect. Right heart blood now passes normally through the lungs returning to the left heart and on out the aorta Left heart and aortic pressures, however, are now higher than those in the pulmonary artery leading to a reversed shunt (left-to-right) of flow from aorta to pulmonary artery (Fig. 7). In consequence, a considerable portion of left ventricular outflow leaks back into the lungs so that a sizable volume goes round and round from left heart to lungs and back to left heart. The mechanical effect of such in-

TO HEAD AND UPPER EXTREMITIES



TO TRUNK AND LOWER EXTREMITIES

FIGURE 7. Ductus arteriosus abnormally patent after birth showing reversal of blood flow (aorta to pulmonary artery)—diagrammatic.

efficiency, as years go by, is obvious. The left heart must compensate for this lowering of effective diastolic aortic pressure and it does so either by working harder or faster in its attempt to maintain an effective systemic circulation. It, therefore, wears out much earlier than would a normal heart, to account for the greatly shortened life span of patients so afflicted. Left ventricular hypertrophy eventually develops, as does great dilatation of the pulmonary artery, in response to its unnatural environment of high-pressure blood flow. Death results then from either heart failure or subacute bacterial endocarditis, the latter infection becoming superimposed on the strained and traumatized tissues of the ductus at the pulmonary artery. Occasionally, rupture of the ductus or of the aneurysmal dilatation of the pulmonary artery is responsible for sudden disaster. One of the great contributions to surgery and mankind has been the development of a simple and effective method to interrupt this vicious cycle of events.

Clinical Findings: The average-sized ductus gives rise to few, if any, symptoms during childhood. Its presence is usually detected by discovering a murmur during an acute illness or at routine examination. The knowledge that their child has a heart murmur may then lead the parents to suspect minor deviations from their other normal children. Growth and

development, as a rule, are within normal limits although after surgical correction the child will usually develop more rapidly, an indication that *insidious and unrecognized changes had been present. Cyanosis is absent.* Dyspnea, palpitations, and exercise intolerance are not noted until early adult life when congestive heart failure is an ever-present threat.

The cardiac findings are usually very characteristic and diagnostic. There is a continuous murmur through systole and diastole, located maximally in the second left intercostal space, transmitted upward into the supraclavicular area. It has the quality of "running machinery," and a "humming top" or a "train in a tunnel." An associated thrill is frequently present. Very occasionally the systolic or diastolic component of the murmur may be faint or absent, making it difficult to be certain of the diagnosis on auscultatory grounds alone. A widened pulse pressure (normal systolic and lowered diastolic pressure) develops according to the size of the shunt and the age of the patient.

Supportive Data: Fluoroscopic and x-ray examination, when carefully performed, will demonstrate prominence of the pulmonary artery markings, and the increased pressure in these vessels may almost be visualized by the vigorous pulsations at the hilus of the lungs (hilar dance). The pulmonary artery-conus segment of the left cardiac border may be prominent.

The electrocardiogram is usually normal. In older patients some evidence of left ventricular strain may be seen. Right axis deviation is rarely, if ever, seen unless there be some additional cardiac anomaly to complicate the picture.

Angiocardiography is of little or no value unless the opaque dye is introduced directly into the aorta above the lesion. Rarely the ductus may be outlined in this manner, but most commonly the presence of a ductus can only be suspected by observing simultaneous opacification of the aorta and the pulmonary artery. The findings of an increased pressure in the pulmonary artery and a localized increase in its oxygen content by cardiac catheterization is further corroboratory evidence.

Surgical Technic: Ligation or division of the patent ductus, as perfected and practiced since 1938, *results in a surgical "cure" provided resort to* operative intervention has been made before the heart and great vessels have become too greatly damaged. The operative mortality in childhood should not exceed one per cent. In patients with secondary complications, such as actual or impending heart failure, subacute bacterial endocarditis, and the like, the mortality may be somewhat higher. For this reason the diagnosis of patent ductus arteriosus in a child over the age of two is considered indication enough for surgical correction without further delay. The presence or the history of subacute bacterial endocarditis demands early surgery after a suitable period of antibiotic sterilization has elapsed.

In 1907, Munro delivered a treatise before the Philadelphia Academy of Surgery entitled "Ligation of the Patent Ductus Arteriosus" in which he made a plea for greater diagnostic efforts in this condition. Although he even presented in detail an acceptable surgical approach, it was not until 1938 that Strieder made the first courageous attempt on the living

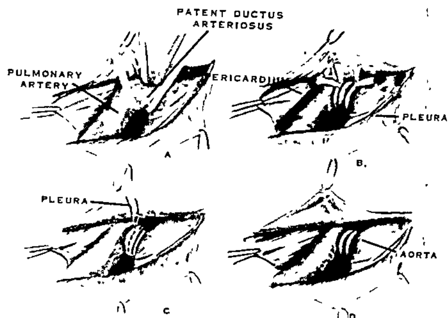


FIGURE 8 Surgical obliteration of patent ductus by the multiple ligation method (transfixion suture through the middle).

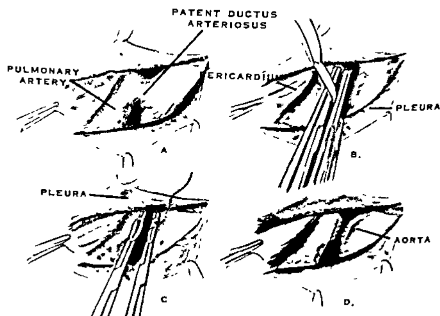


FIGURE 9. Surgical division of patent ductus arteriosus

patient demonstrating that the operation was certainly feasible. The second such patient was operated upon later in the same year by Gross who firmly established the procedure and subsequently refined his technic to *insure maximum safety and excellence of results.*

Ligation Technic: The left chest is opened widely to gain exposure of the hilus of the lung and the superior mediastinum. The pleura overlying the vagus nerve, in the region of the aortic arch, is incised. The left pulmonary artery and the recurrent laryngeal nerve can be identified by locating the point of maximal thrill which always lies over the pulmonary artery. The nerve is carefully isolated and retracted away from the ductus which is, in turn, dissected from its surrounding fibrous attachments for the placement of ligatures. Two small umbilical tapes are tightly tied, one at the aortic end and the other at the pulmonary artery end of the ductus. One or more transfixion suture-ligatures are placed through the central portion (Fig. 8).

Division and Suture Technic: While the general approach to the ductus is the same, it is usually necessary to isolate the ductus, left pulmonary artery, and adjacent portions of aorta more completely and to clean these structures thoroughly of all areolar attachments Actually, for best results the identical technic should be carried out when ligation is contemplated. This then permits the application of a pair of specially devised ductus clamps, one close to the aorta and the other close to the pulmonary artery. These clamps will not easily slip nor will they crush the vessel. The ductus is divided and the two free ends are closed with continuous arterial silk (Fig. 9).

In recent years the trend has been toward division of the ductus because of the possibility (remote, when properly performed) of recanalization of the ductus ligated in continuity. On the other hand division of the ductus may be somewhat more hazardous, especially in the hands of the occasional operator, leading to a higher mortality. The procedure most easily, safely, and completely performed by the individual surgeon is the procedure of choice.

(b) Coarctation of the Aorta

Definition: Coarctation of the aorta is a congenital stenosis, complete or partial, usually found in the descending arch just distal to the subclavian artery. It is frequently associated with the ductus or ligamentum arteriosus. This anomaly was first described in 1761 by Morgagni (Fig. 10).

Pathology: There are two varieties of aortic coarctation, the infantile and adult types. The infantile type is less common, occurring in not more than five per cent of cases. It is seen primarily in the newborn or the very young and is commonly associated with other congenital abnormalities. It is characterized by a long and diffuse narrowing of the aortic segment involved and often is more proximally located than is the adult type The aortic isthmus, that area between the insertion of the ductus and the subclavian artery, is the area involved. However, the narrowing may include the entire transverse arch and extend, at times, down into the ascending

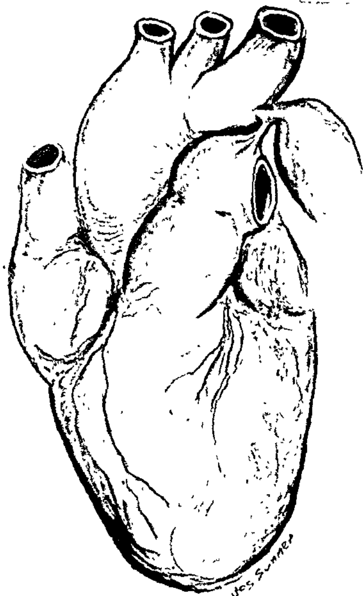


FIGURE 10. *Heart and great vessels to show the anatomical location of coarctation of aorta (adult type).*

portion. Occasionally, the ductus arteriosus will be patent and when this is the case, should the coarcted area lie proximal to the ductus, lower extremity cyanosis is present.

In the adult form, the obstruction involves a much shorter segment of aorta, is most often seen at the insertion of the ligamentum arteriosus and is the usual type seen in the older patient. Very rarely the ductus arteriosus may be patent in this group and, when this is true, the coarcted orifice may be quite small. In some of such cases the stenosis is complete.

Rather typical changes are seen in the artery above and below the point of constriction. Proximally, due to the excessive pressure produced by the

block, dilatation, thickening of the aortic wall, and early degeneration and sclerosis are present in the aorta as well as the subclavian artery. With incomplete obstruction, varying degrees of thin walled post-stenotic dilatation, without the sclerotic changes, complete the picture.

The cardiac effect of the lesion is an increased work load on the left ventricle and left ventricular hypertrophy is noted in approximately seventy-five per cent of cases.

The blood supply to the trunk and lower extremities is maintained by an extensive collateral circulation circumventing the aortic obstruction through the upper intercostal arteries from the subclavian artery giving rise to anastomotic channels around the shoulder and scapula and on into the internal mammary and deep epigastric arteries.

Incidence and Prognosis: In Abbott's series of 1000 cases of congenital defects of the cardiovascular system, 142 coarctations of the aorta were found. The adult form was commoner than the infantile form by five to one and males predominated four to one over females.

Seventy-five per cent of the untreated cases will die as a direct result of the hemodynamics of the aortic obstruction. The usual causes of death are rupture of the aorta from dissecting aneurysm and cardiac decompensation. Other complications are cerebral hemorrhage and endarteritis or endocarditis. The average age of death in patients untreated surgically is thirty-two.

Symptoms: There are many patients with a mild or moderate form of obstruction who have very few if any symptoms In the more severe forms of coarctation headache, vertigo, palpitations, and blurring of vision on exertion may be the presenting complaint. Due to the diminished blood flow in the lower extremities, claudication and paresthesias will often develop as a part of the clinical picture.

Diagnosis: The most important physical finding leading to the diagnosis of coarctation of the aorta is upper extremity hypertension and hypotension or no recordable pressure in the legs Full and bounding pulses in the arms and markedly diminished to absent pulses in the lower extremities complete the picture.

Evidence of the marked collateral circulation compensating for the obstruction should next be sought. This is noted over the interscapular region where definite pulsations, easily palpable, will be found and in many instances a systolic bruit can be heard just medial to the border of the scapulae.

A systolic murmur is usually heard over the upper precordium and is transmitted to the axilla and/or may be audible over the back.

The roentgenogram will confirm the presence of the collateral circulation by showing a notching or scalloping of the inferior edge of the ribs. Additional x-ray evidence of coarctation, often overlooked, is the lack of a prominent aortic knob in the PA projection. Increase in the size of the left ventricle will be noted in the majority of the older cases of severe obstruction. However, in the younger patient the notching of the ribs and left ventricular enlargement may not be present by radiographic examination.

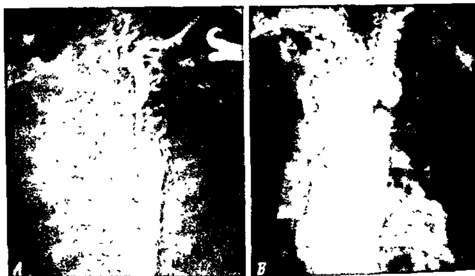


FIGURE 11. Direct aortography illustrating two types of coarctation of the aorta. A, The infantile type which the aorta below the left subclavian artery is atrophic for a considerable length. B, The adult type showing a more localized stricture of the aorta at the level of the obliterated ductus arteriosus. Note the tremendous dilatation of the internal mammary arteries (collateral circulation).

Electrocardiographic changes of left ventricular preponderance will aid in the overall picture in the older cases where the increased work load has been present over a long period of time.

Final confirmation can be afforded by the use of retrograde aortography. This is accomplished by injecting the contrast media directly into the proximal aorta through the brachial artery. Care should be taken during injection of the dye to protect the brain by hyperoxygenation and tem-

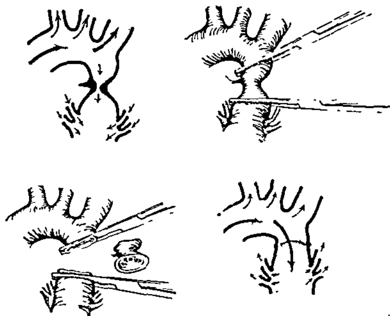


FIGURE 12. Surgical resection of the coarcted segment and end-to-end anastomosis.

porary carotid compression. Aortography is by no means necessary for the accurate diagnosis of coarctation of the aorta but will give useful added information as to the length and exact location of the stricture and will aid in detecting the presence or absence of associated congenital abnormalities (Fig. 11).

Treatment: At the present time the surgical relief of coarctation of the aorta is relatively simple and is a curative procedure. In most of the cases resection of the coarcted segment and end-to-end suture of the divided aorta can be accomplished (Fig. 12).

In the longer types it may be necessary to bridge the defect with a preserved homograft. Since there are now several acceptable methods for preserving vascular tissues, grafting in this area is done with facility. Prior to the time when grafts were readily available the left subclavian artery was sacrificed and turned down to restore continuity to the aorta. Since this has proved to be an inadequate method the preferred technic today is grafting.

The optimum time for operation is between the ages of seven and fifteen years before extensive and possibly irreversible cardiovascular changes have developed. While cases in the fourth decade have been successfully operated upon, the risk is materially greater due to the marked degenerative changes in the arterial wall seen after this lapse of time. In capable hands the mortality should not exceed five per cent in uncomplicated cases of coarctation of the aorta.

II. Intracardiac

(a) Pulmonary Stenosis

Definition: Pulmonic stenosis is an obstruction of the pulmonary arterial system at or just proximal to the pulmonary valve.

Synonyms: Pulmonary valvular stenosis; "pure" pulmonary stenosis; pulmonary stenosis with intact interventricular septum; pulmonary stenosis with patent foramen ovale, etc.

Pathophysiology: Pulmonary stenosis may be due to a general narrowing of the outflow tract of the right ventricle (called the pulmonary conus or infundibulum of the right ventricle) or, much more commonly, is due to a congenital fusion of the pulmonary valve leaflets into a small cone or megaphone-like diaphragm. In this condition there is an intact ventricular septum and no malposition of the aorta, which arises normally from the left ventricle. Therefore, all egress of blood from the right ventricle can only be made through the stenotic pulmonary valve. Thus, as the entire blood flow must pass through the pulmonary artery on its way to the lungs, there is no shunt of right heart blood (venous or unoxygenated) into the left heart or systemic circulation. Hence, there is no peripheral oxygen unsaturation and cyanosis is not present (Fig. 13).

As the otherwise normal child grows and becomes increasingly active, the right ventricle experiences progressively greater difficulty with the discharge of the returning circulation through the tiny, unyielding pulmonary orifice. Great dilatation and hypertrophy of the right ventricle gradually ensues. Eventually, this leads to insufficiency of the tricuspid valve and

to a similar congestion and distention of the right atrium. Should the *foramen ovale,* in a given instance, remain as an overlapping valve, rather than closed by fusion, dilatation and patency of this *structure may develop.* With right atrial pressures unnaturally as high, or *higher than* those in the left atrium, a right-to-left shunt may result. Unoxygenated blood then mixes with the returning flow from the pulmonary veins within the left atrium and is pumped out through the left ventricle and aorta producing a constant or intermittent cyanosis especially enhanced by ex-

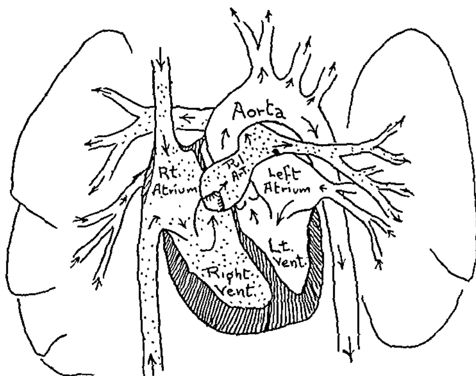


Figure 13 Diagrammatic representation of pulmonary valvular stenosis with post-stenotic dilatation of the pulmonary artery.

ercise. It is to be emphasized and remembered that this phenomenon is purely a secondary one resulting from long standing, unrelieved pulmonary stenosis and is not considered an integral part of the clinical entity of pulmonic stenosis, as it is commonly seen.

Clinical Findings: As a rule, such a patient is asymptomatic until early adolescence when exercise intolerance becomes noticeable. Prior to this, the typical precordial systolic murmur most prominent in the second and third interspaces on the right will have been noted at the time of routine physical examination. A faint thrill may be detectable. Dyspnea and incapacity are usually progressive.

Supportive Data: Radiographically, the cardiac silhouette becomes enlarged particularly to the right. The pulmonary artery-conus segment of

the left cardiac border becomes increasingly prominent. Great dilatation of the pulmonary artery (post-stenotic), beyond the point of valvular obstruction is evident. The pulmonary lung fields may show diminution of the normal vascular markings. Fluoroscopic evaluation will show the enlargement of the cardiac chambers on the right in contrast to their normal sized neighbors on the left. Angiocardiography, if desired, will more clearly delineate these salient features.

The electrocardiogram will reveal a right axis deviation.

Cardiac catheterization demonstrating abnormally high pressures within the right ventricle, as compared to the much lower readings within the



FIGURE 14 Pulmonary valvulotome introduced through the right ventricle dividing the stenotic valve cone Insert shows the bicuspid nature of the divided pulmonary valve cone

pulmonary artery (in the absence of a demonstrable intracardiac shunt—normal oxygen saturations), will clinch the diagnosis.

Surgical Technic: Direct intracardiac pulmonary valvulotomy, as originally suggested and attempted by Doyen, revived by Sellors, and popularized by Brock is today the surgical treatment of choice. This method employs a small transventricular (right) incision through which a diamond-shaped knife is introduced into the fused pulmonary valve cone dividing it into two symmetrical leaflets (Fig. 14). The bicuspid valve, so produced, can open and close in response to ventricular systole and diastole, thus adequately relieving the obstructed valve without the production of significant insufficiency. Several hundreds of these operations have been performed throughout this country and Europe. The mortality rate in well directed clinics is considerably below five per cent. Provided surgery is undertaken at an early age, before the heart and vascular system have been permanently and adversely affected, preferably under ten years, the results are highly satisfactory. (See section D—Extracorporeal circulation and corporal hypothermia.)

Rarely, pulmonary obstruction of this type may occur in the infundibulum of the right ventricle proximal to a normal pulmonary valve. Such an obstruction can also be treated satisfactorily by direct infundibular resection as described below under the tetralogy of Fallot. Ten such cases have been operated upon by the authors with a successful outcome in each.

(b) The Tetralogy of Fallot

Definition: A combination of congenital intracardiac defects, originally grouped into an entity by Fallot, consisting of pulmonary stenosis (infundibular or valvular or both), a high interventricular septal defect, dextroposition (to the right) of the aorta, sometimes called an over-riding aorta (straddling the incomplete ventricular septum) and concomitant hypertrophy of the right ventricle.

Synonyms: The tetralogy; pulmonary stenosis with ventricular septal defect; "blue baby."

Physiological Considerations: Obstruction to the flow of blood into the pulmonary artery (pulmonary stenosis) is most commonly associated with the syndrome known as the tetralogy of Fallot. Were this obstruction complete, and both atrial and ventricular septa normally closed, the fetus, with such a malformation, would die *in utero,* for his returning circulation would have no outlet. In this condition, however, the entire embryonal development of the right ventricular outflow tract and the roots of the great vessels (pulmonary artery and aorta) is deficient. As a result the ventricular septum, which normally divides the right and left ventricles, remains incomplete at its upper pole. Thus, the pulmonary artery and aorta which arise side by side at the upper end of the ventricular septum and normally are separated by it, have, *in effect,* a common orifice. The root of the aorta which, under normal conditions, arises well down within the outflow tract of the left ventricle finds a portion of its right wall absent so that it becomes as much a part of the outflow tract of the right ventricle as the left. In consequence, due to the high ventricular septal

defect, the aorta is described as being shifted to the right (dextroposition) or in more descriptive terms, an over-riding aorta, for it lies astride the incomplete septum—part on the left side and part on the right. From the standpoint of survival of the fetus this might be described as a fortunate circumstance for it provides an easy avenue of escape for right ventricular blood otherwise hampered by the pulmonary obstruction.

Because of this abnormal shunting of blood from right to left there is a *greatly diminished blood flow through the lungs* (Fig. 15). This is of

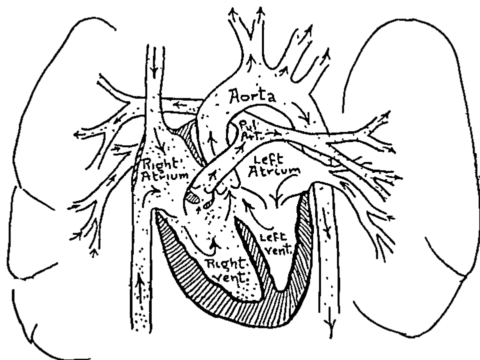


FIGURE 15 Diagrammatic representation of the course of blood flow in the tetralogy of Fallot (blood shunting from right to left through interventricular septal defect)

little consequence to the fetus for his blood is oxygenated through the maternal placenta and not by his only pulmonary vascular bed. At birth, however, the fetus finds his nine month period of complacency at an end. He must now fend for himself. His survival now depends, for the most part, on the severity of his pulmonary obstruction for he can only maintain life if the degree of pulmonary blood flow provides sufficient oxygenation to maintain at least the minimal bodily requirement. Should this be insufficent he will die shortly after birth or within a few weeks or months, an event which not infrequently occurs If, however, his pulmonary obstruction and shunt are not too great he may well survive for an indeterminate

period and his functional status will be directly proportional to the degree of effective pulmonary flow.

It goes without saying that such infants are cyanotic from birth and will remain so unless the defect can be corrected or their effects alleviated. As with life in general, every passing day poses new problems and dangers. The infant grows and becomes more active. The right ventricle, normally a thin-walled muscular structure, developing only a low head of pressure sufficient to propel the stream of blood into the equally low pressure lake of pulmonary vascular blood, must now respond to meet its new demands. Not only must it overcome the unnatural barrier of pathologic pulmonary obstruction in its efforts to provide adequate pulmonary circulation, but it must also develop the power to propel its contents into the outflow tract of the left ventricle and aorta where normally the pressures are much higher than those in the right heart. These two forms of obstruction, one structural and one physiological, are for a time compensated for by the development of muscular hypertrophy and dilatation to the point of great enlargement of the right ventricle. This takes place even though the cardiac musculature is being supported by a blood stream greatly deficient in oxygen. True, the infant's blood-forming organs are attempting to keep pace with oxygen want by manufacturing an excess of red blood corpuscles (compensatory polycythemia) but even this effort may eventually defeat its own purpose as the increased viscosity (increased ratio of cells to plasma) of the blood leads to slowing of the blood stream and intravascular thrombosis.

Thus, the co-existence of pulmonary obstruction (stenosis), high ventricular septal defect, dextroposition of the aorta, and right ventricular hypertrophy presents a never ending series of physiological complications which heretofore has only lead to a most precarious existence and death at an early age.

Pathological Considerations: When surgery was first considered for the relief of patients suffering from this condition the present day concepts of a definitive intracardiac approach to cardiac disease had not been developed. As the main underlying physiological defect in the tetralogy is its *diminished pulmonary blood flow*, it was logical that initial surgical efforts should be directed toward this aspect of the problem. The ingenious systemic-pulmonary shunt devised by Blalock and Taussig so beautifully answered the problem that little emphasis was placed upon the pathologic nature of the pulmonary obstruction itself. In the light of more recent developments, however, it is essential that the obstruction within the outflow tract of the right ventricle be more clearly understood.

The infundibulum of the right ventricle is that part of the pulmonary conus area lying immediately proximal to the pulmonary valve In this condition it is commonly the seat of muscular or fibrous hypertrophy, occurring just adjacent to the pulmonary valve (subvalvular), or at some distance from the valve, in which case a small olive-sized or egg-sized chamber may separate the obstructing tissue from the mouth of the pulmonary artery. Such an obstruction is known as infundibular stenosis and the resulting chamber, small or large, the infundibular chamber (third ven-

tricle). The wall of this chamber may be either thin and fibrous or muscular in nature. The pulmonary artery is of normal size or slightly underdeveloped, but the pulmonary valve is usually normal (tricuspid). Functionally the valve is patent and competent in most instances. Direct intracardiac resection of such an infundibular stenosis is now practical and events are proving that this may be the surgical technic of choice for the relief of patients so afflicted rather than resort to extracardiac vascular shunts

Much less commonly, the entire infundibulum may be hypertrophied and present itself as a long, muscular chamber proximal to the pulmonary valve. Even in these, there is usually one point where the obstruction is maximal and resection at this location may relieve the patient. This type presents greater technical difficulties than do those described above and the operative mortality is higher.

Rarely there is a high degree of pulmonary artery hypoplasia with both valvular distortion and infundibular stenosis lying immediately subvalvular in a narrow muscular channel. Such pathology defies the direct approach and a shunt procedure must be carried out for best results.

A number of cases of the tetralogy of Fallot are said to have valvular stenosis similar to that described under pulmonary valvular stenosis without accompanying infundibular stenosis Pulmonary valvulotomy can be easily carried out as described above. Although stressed by others, the authors have rarely observed this type of pathology in the tetralogy of Fallot.

Clinical Findings: Clinically, all of the above mentioned pathologic types are similar. Likewise, a number of other combinations of defects with pulmonary stenosis and ventricular septal defect such as the three chambered heart (single atrium or ventricle), tricuspid atresia (briefly discussed below), the Eisenmenger complex (referred to below), and others may have an almost identical clinical picture.

Cyanosis is present at birth, although in isolated instances it may not be obvious for some weeks or months The degree of cyanosis depends upon the amount of unoxygenated blood in the peripheral circulation (five grams of reduced hemoglobin are necessary to produce cyanosis) which in turn depends upon the degree of stenosis, the degree of aortic displacement and the amount of compensatory polycythemia In certain instances an additional patent ductus arteriosus may be present which temporarily, at least, may increase the pulmonary flow to non-cyanotic levels. Should the ductus gradually close after several months marked increase in cyanosis and in all symptoms may develop even to the point of a rapid fatality. Some patients may not be cyanotic at rest but develop cyanosis on exertion.

Clubbing of the fingers and toes is evident when severe cyanosis has been present for several months. Watery suffusion of the conjunctivae presenting a "blood shot" appearance is a common finding. Marked limitation of activity and endurance, easy fatigue, the desire to lie down in the midst of some intriguing game is noted in most instances Some can walk several blocks but many can only take a few steps. The increase of cyanosis

and dyspnea with exercise brings on the characteristic "squatting" position assumed by so many of these children. Apparently this position makes their respiratory effort more effective. As the patient's condition deteriorates paroxysmal attacks of dyspnea may appear either spontaneously or after exercise of mild degree. Temporary unconsciousness or convulsions may develop. As the polycythemia and hematocrit increases (sometimes to the level of eight to ten million red cells) vascular thrombosis may occur and peripheral evidence of a cerebral vascular accident may be present. Such developments call for the administration of oxygen, possibly venesection, or the administration of plasma or glucose solutions in an attempt to "dilute" the blood viscosity. Dehydration is to be avoided during the acute phases. It is the rare child who lives to young adulthood unless this pernicious chain of events can be interrupted by surgical intervention.

Supportive Data: Routine radiologic examination in most instances will reveal the classical boot-shaped silhouette with its elongated goose-necked configuration in the region of the great vessels caused by the concavity of the pulmonary salient (small pulmonary artery). The apex of the heart is turned upward due to elevation of the left ventricle and cardiac apex by the hypertrophy of the right ventricle. The parenchyma of the lungs appears clear because of the diminutive pulmonary vascular markings. Fluoroscopic examination will confirm these findings and there will be no visible pulsations of the vessels (pulmonary) in the hilar areas. While this description is that found in most cases there may be many variations from this pattern especially in the infant.

Angiocardiography is often of the greatest help, for with injection of the contrast media there will appear a simultaneous opacification of the aorta and pulmonary artery, unequivocal evidence of a right-to-left shunt through the interventricular septal defect. Indeed, there may be very little evidence, or a considerable delay, of diodrast in the pulmonary artery if the stenosis is marked. Delineation of the exact position and type of stenosis is rarely possible by this study although on occasions the infundibular chamber will be recognizably outlined.

Catheterization of the right heart will reveal the large right ventricle and its increased intraluminal pressure. If the catheter can be passed through the stenotic area into the pulmonary artery, the pressures will fall sharply, ofttimes to very low levels. Commonly, the pulmonary artery cannot be entered. Not infrequently, the catheter will be observed to pass through the high ventricular septal defect into the overriding aorta, giving immediate visual evidence of the anatomical abnormality.

The electrocardiogram almost invariably shows a right ventricular hypertrophy by a shift of the vertical axis to the right. The circulation time is characteristically short (arm to tongue) because the overriding aorta permits direct passage of blood from the right ventricle into the systemic circulation without the normal delay in the pulmonary circuit. Peripheral arterial oxygen saturations will reflect the shunt, varying, from thirty to eighty per cent of normal saturation at rest, frequently dropping

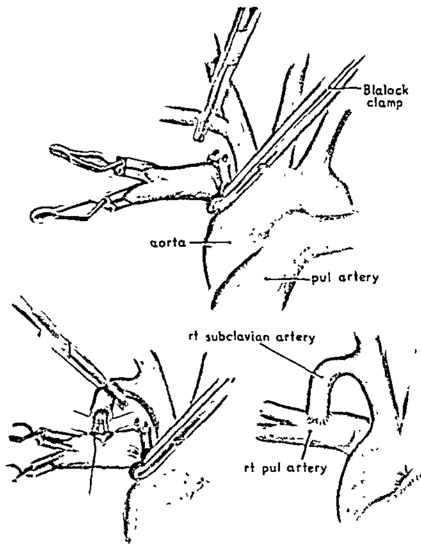


FIGURE 16 The Blalock-Taussig shunt with anastomosis of the right subclavian artery into the right pulmonary artery (diagrammatic).

even from this low level with exercise. This latter finding may almost be diagnostic, for few, if any other, anomalies will produce this sign.

The tetralogy of Fallot must be differentiated from other forms of congenital cyanosis, as mentioned, particularly the so-called Eisenmenger complex. In this malformation, dextroposition of the aorta and a high interventricular septal defect are present but pulmonary stenosis is absent. Excessive pulmonary blood flow during infancy would seem to be the underlying physiologic cause.

Surgical Technics: Prior to the epoch-making surgical treatment proposed and carried out by Blalock and Taussig in 1945, there was little to

offer these individuals. Limitation of activities, oxygen as needed for paroxysmal dyspnea, digitalization, venesection, and the administration of fluid with anticoagulants when vascular thromboses threatened or developed constituted the only available therapeutic approach. Few lived to adult life.

Blalock and Taussig devised an extracardiac shunt whereby the cut end of the right subclavian artery (systemic vessel from left heart) is anastomosed into the side of the pulmonary artery (pulmonary circulation from right heart) (Fig. 16). By this means the mixed venous-arterial aortic blood, much of which has by-passed the lungs, is redirected into the pulmonary vascular bed where its more complete oxygenation effectively relieves the clinical manifestations of dyspnea and cyanosis. Thus, an additional (fifth) defect has been added to four already present—a "patent ductus arteriosus" has been created. Several thousands of these operations have been performed the world over with a high degree of clinical success. The operative mortality, excluding the early experimental days, is now approximately ten to twelve per cent despite the precarious condition of these tiny sufferers.

Utilizing the same underlying physiologic principles, Potts and Smith modified the Blalock technic by performing a direct side-to-end anastomosis between the aorta itself and the pulmonary artery on the left. This was accomplished by the development of a special clamp which encircles the aorta but excludes a portion of its wall from the uninterrupted flow of aortic blood. Whereas this method has the technical advantage of the use of at least one larger vessel (aorta *vs.* subclavian artery) in the performance of the anastomosis, and by so doing enables the surgeon to operate upon younger children when necessity demands, care must be taken to avoid the production of too large a shunt which might suddenly flood the pulmonary circuit. Attention to detail (4 to 5 mm. size of opening) as cautioned by Potts will obviate this catastrophe. On the other hand, the Blalock shunt cannot be larger than the diameter of the subclavian artery which in most instances has been found to be the proper size. In infants under the age of two, however, the subclavian artery will usually be too small for routine anastomotic usage. The results of this modification in technic are similar to those described above.

Without detracting in the least from these brilliant achievements, for indeed, they have been the pacemakers in the recent renaissance of cardiovascular surgery, there are certain obvious objections to the production of shunts between the arterial and venous circulations even though they may temporarily improve the condition under consideration. As stated, a "patent ductus arteriosus" has been created, a defect which, were it to be found in existence alone, would demand early surgical obliteration. The late effects of such an arteriovenous fistula on the heart and circulation are well known, and although in this particular instance the already present interventricular septal defect (also an A-V fistula) may conceivably counteract in some measure the deleterious late effects of an artificially produced ductus, there is certainly cause for real concern as to the eventual fate of a patient harboring so many unphysiologic anomalies. Would it



FIGURE 17. Direct intracardiac resection of a portion of the infundibulum in the tetralogy of Fallot is initiated by Brock. Infundibular resecting forceps inserted through right ventricle Insert shows forceps in place (Glover modification).

not be better to focus attention upon methods designed to rid the patient of his defects, insofar as it is feasibly possible, rather than to add to them? Such has been the proposal of Brock who has devised a means of improving the pulmonary circulation by the direct, intracardiac removal of the original pulmonary obstruction (infundibular hypertrophy). In this way existing defects are removed rather than compensated for by the addition of others.

The Brock technic calls for intrapericardial exploration of the right ventricular outflow tract and the main pulmonary artery. In the authors'

experience the point of obstruction will most often be located beneath the myocardium proximal to the orifice of the pulmonary artery. Its exact location can be delineated by finger palpation and gentle intraluminal probing with a tiny, urethral-like sound. A small incision is made through the myocardium overlying the point of obstruction, a specially devised resecting instrument inserted and a portion of the obstructing ridge excised (Fig. 17). Thus, a more normal type of circulation can be re-established and the right-to-left shunt materially diminished. True, the overriding aorta and ventricular septal defect remain untouched, but their physiologic effect is now minimized for the right-heart blood will seek the path of least resistance—that into the low pressure pulmonary vascular bed. Oxygenation will now be more complete and the patient's clinical condition is improved accordingly.

Should the point of obstruction be found in the pulmonary valve, the simpler technic as described under pure valvular stenosis is employed. If, however, initial exploration fails to identify readily the point of obstruction, or should there be extreme hypoplasia of the pulmonary artery, the pericardium is closed and resort is made to the performance of either the Blalock or Potts shunt procedures. Rarely, due to the diminutive size of all available vessels, if even a shunt cannot be fashioned, the suggestion of Barrett is utilized. By removing a portion of parietal pleura, synthesis of the lung and chest wall is promoted in the hope that inflammatory anastomoses between the thorax and mediastinum on the one hand, and the vessels within the pulmonary parenchyma on the other, will develop. This process may be stimulated by rubbing the lung surface with gauze or by the application of talc or powdered asbestos. An occasional surprising result can be obtained by this maneuver.

Although several hundreds of cyanotic children have been surgically managed by the direct intracardiac approach as described, with initial mortality and clinical results equal to, or even surpassing, those of the shunt procedure, one must fully realize that more time must elapse before the principles and practice of this technic will find its rightful place in the overall surgical treatment of the "blue baby." (See section D—Extracorporeal and Corporal Hypothermia.)

(c) Tricuspid Atresia

The tricuspid valve is seldom the site of serious, primary pathologic lesions. When, on relatively rare occasions, it is in a state of congenital atresia, there is usually an associated interauricular septal defect and a hypoplastic right ventricle. In such situations the pulmonary artery arises either from the left ventricle or more commonly, from the rudimentary right ventricle, and pulmonary stenosis is present.

The clinical effect of such distortion is the cyanotic child resulting from the intracardiac passage of unoxygenated venous blood directly into the systemic circulation *via* the left atrium, ventricle, and aorta. Such a patient may clinically be indistinguishable from the common variety of "blue baby" (tetralogy of Fallot) except by angiocardiography or cardiac catheterization or both.

Angiocardiography will reveal early simultaneous opacification of the right and left atria, absence or diminution of the right ventricular shadow, together with the features of opacification of the aorta and pulmonary artery. This pattern may not be essentially distinguishable by present technics from that seen in the tetralogy of Fallot. Coupled with the electrocardiographic observation of left ventricular hypertrophy and preponderance the diagnosis may be clarified.

Cardiac catheterization should reveal the presence of tricuspid obstruction and the atrial septal defect.

In this instance, due to the multiplicity and nature of the deformity, the only acceptable form of surgical treatment at present is the production of a systemic-pulmonary shunt. The results obtained, although not entirely satisfactory, offer considerable palliation and relief of clinical signs and symptoms. Not infrequently the interatrial septal defect, always present, will require further enlargement to properly handle the rearranged circulation produced by the shunt.

Tricuspid stenosis, resulting from rheumatic disease, has been described as a pathologic entity. Upon occasion it has been diagnosed with accuracy during life, and a number of surgical corrections have been accomplished. Its surgical relief does not present great difficulties for it can be accomplished by finger and guillotine through the right auricular appendage in a fashion similar to that described below for mitral stenosis.

(d) Septal Defects—Auricular and Ventricular

Interatrial and interventricular septal defects are among the most common of congenital cardiac defects In many instances they are not of great significance. This is especially true when they are small (as many of them are) and not associated with other cardiovascular anomalies. The prognosis in such cases is said to be excellent and, indeed, many of them are detected only at the time of postmortem investigation of death caused by some totally unrelated condition. In a large number, however, the defects are large or so placed as to create great havoc with the effective mechanics of the circulation leading to invalidism and a shortened life span. It is this aspect of the problem which has stimulated recent surgical investigation.

Atrial Septal Defects: Embryologically there is a normal communication between the two atria known as the foramen ovale (ostium secundum). In the absence of an effective and essential pulmonary fetal circulation, considerable right atrial blood escapes through this foramen into the left heart and out into the systemic circulation (right-to-left shunt). At birth, or shortly thereafter, when respiration establishes a more normal pulmonary blood flow, pressures within the left heart become considerably higher than those in the right. The semilunar valve-like cusps of the foramen ovale then become approximated by the continuous left-sided pressure and so remain throughout life, most frequently to become fused and obliterated after a year or two. Should fusion fail to occur, any condition—cardiac or pulmonary—which sufficiently raises the intraluminal right atrial pressure to levels greater than those within the left atrium, can lead to a right-to-left shunt with its attendant cyanosis. Such a shunt

then becomes a compensatory escape mechanism for entrapped blood. Obviously, any surgery under these circumstances must be directed toward relief of the point of obstruction "up ahead" rather than to the closure of the patent foramen ovale which would result in physiologic disaster (example—pulmonary valvular stenosis).

When one refers to atrial septal defects, in the clinical sense, the term is applied to those defects of the septum other than a patent foramen ovale. These are of two general varieties. Due to defective development of the atrial septum openings may remain in any location. These are usually small and often are not the seat of significant cross-shunting of blood. They occur as a single defect, as a rule, or may be found in asso-

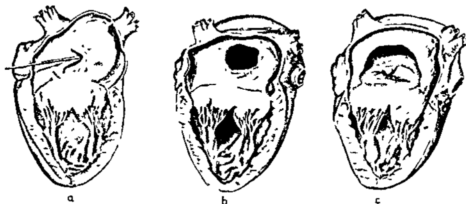


FIGURE 18 Types of interatrial septal defects—diagrammatically viewed from right side. *a*, Simple patent foram
b, Simple interatrial septal defect
defect extending down to the leve
primum)

ciation with a more serious and larger defect—the persistent ostium primum This latter type is occasioned by the failure of closure of the first primitive opening in the atrial septum. It lies in the base of the atria, in the inferior (caudal) aspect of the septum, just above the mitral and tricuspid valves. Left-to-right shunts enormously increase the flow of blood through the right side of the heart and the pulmonary circuit result, leading to right heart failure in early adult life. It is this type of anomaly with which the surgeon must be prepared to cope if he is to render real service in the solution of the overall problem (Fig. 18).

Various methods, both experimental and clinical, have been suggested and carried out for the closure of atrial septal defects. Experimentally, Cohn pushed the right atrial wall into the defect to plug the opening, suturing the inverted wall to the septum. Murray passed mattress sutures of silk or fascia through the heart from front to back in the plane of the septum. The partial block of the opening so obtained, either as a lattice-work or by drawing the sutures tightly to approximate the anterior and posterior myocardial wall, was somewhat effective but hardly can be expected to give complete satisfaction. Swan inverted the right and left auricular appendages to meet each other at the point of the atrial defect,

holding them in this unnatural position by a series of mattress sutures and plastic buttons. Such inversion greatly reduces the functioning lumen of the atria and the returning blood flow to make this method of questionable routine clinical value. Hufnagel has devised plastic buttons which when screwed together within the atria, the one on the left atrial side and the other on the right, effectively close those defects which have a complete free rim around their periphery similar to those produced in the experimental animal. Unfortunately, the majority of human defects do not provide such a complete rim and hence their applicability to human use is limited. The development of extracorporeal pump-oxygenators in which it is hoped that intracardiac blood can be temporarily diverted, allowing septal closure by patch or suture under direct vision, has not yet reached the stage of perfection required to make the procedure safe for successful clinical application. The authors have demonstrated experimentally that pedicled tube flaps of pericardium can be drawn through smaller defects in an oblique manner from the superior aspect of the right atrium to the anteroinferior aspect of the left atrium. Such tissue remains as a living structure and becomes incorporated into the septal walls as a viable plug without encroachment upon the cardiac chambers or the circulatory flow. Bailey has modified the procedure suggested by Cohn to include the insertion of the index finger through the right auricular appendage to guide the placing of sutures between the atrial wall and septum. Gross has developed a rubber "well" which, when sutured around the periphery of the opened right auricular appendage, provides access, through its contained column of blood, to either direct palpatory suture or the placement of a patch (pericardium, plastic material, etc.) to close the offending defect.

It is sufficient to state that at this time, even though a great many human patients have been operated upon by one or more of these several procedures and with complete closure, no standardized technic has been adopted to the exclusion of all others and the method employed presently remains the one preferred by the individual surgeon. The authors prefer the method of purse-stringing the interatrial septum as described by Sondergard and refined by Bjork. This method will successfully close all defects of the ostium secundum type but is not adaptable to the closure of an ostium primum. Indeed, no method at present can routinely close an ostium primum.

Ventricular Septal Defects: Much of what has already been said concerning defects of the interatrial septum can be applied equally to those of the interventricular septum Again, two types have been recognized. Simple perforations of the septum occurring at any level (Roger's disease) are, as a rule, relatively small. Although a harsh systolic murmur may be heard readily maximally just to the left of the sternum in the third and fourth interspaces, there is seldom enlargement of cardiac size and rarely is there physical incapacitation No cyanosis is present as the shunt is from left-to-right.

Should the defect be large or should it be located high in the septum (as an appreciable number are), just proximal to the orifices of the great

vessels, clinical disability will eventually result. High interventricular septal defects are caused by the failure of the ventricular septum from below and the aortic septum from above to meet. In these a very considerable left-to-right shunt may develop, forcing blood under high pressure out through the pulmonary valve, producing dilatation of the pulmonary artery. Pulmonary parenchymal changes may occur as in the Eisenmenger complex, leading to dyspnea and cyanosis.

An increasing number of interventricular septal defects are presently being closed in a highly satisfactory manner by open heart, direct vision surgery. The development of such surgery employing total cardiac bypass has reached its greatest efficiency in the hands of Lillehei and associates and Kirklin, each of whom reported outstanding results in this newest and most dramatic form of cardiovascular surgery. (See section D—Extracorporeal Circulation and Corporal Hypothermia)

(e) Transposition of the Great Vessels

Complete transposition of the great vessels implies that the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. Under such circumstances blood returning to the right heart passes directly into the aorta, completes the systemic circuit and returns again to the right heart The pulmonary circulation returns to the left heart, passes out the pulmonary artery and back again into the left heart. Thus, two separate and distinct circulations are present.

This state of affairs is compatible with life *in utero* as oxygenation is provided through the placenta. At birth, however, should no communication exist between the two circulations death is immediate. Survival of many of these infants occurs because there is sufficient shunting of blood to maintain minimal oxygen requirements. A small interatrial septum is most frequently present although the shunt may also be provided by an interventricular septal defect, a patent ductus arteriosus, by insertion of one of the pulmonary veins into the right atrium, or by some combination of these anomalies. At best, the life of such patients hangs in the balance.

Cyanosis is either present at birth or develops shortly thereafter. Dyspnea is always marked with minimal exercise and most commonly rapid respiratory effort is noticed even at rest. Inevitably, progressive cardiac enlargement ensues with engorgement of the pulmonary and hepatic circulations. It is a rare patient who will survive to early adult life, the greatest toll being taken within a few weeks or months after birth.

A systolic murmur over the precordium is usually audible. Roentgen examination will reveal a heart enlarged, both to the right and to the left, with increased pulmonary vascular markings. The electrocardiogram, as a rule, is indicative of right ventricular hypertrophy.

Any combination of defects so gross as that just described may present insurmountable diagnostic difficulties. Under certain circumstances, especially when there is an associated pulmonary stenosis as well, it may be impossible to differentiate from the tetralogy of Fallot. For this reason a number have been subjected to Blalock's systemic-pulmonary-artery shunt. The result has been ineffectual. A few have been improved somewhat by

the creation of an auricular septal defect (over and above that already present) in addition to the extracardiac shunt. Many other ingenious and exacting cross shunts have been devised and attempted without outstanding success so that at present no routinely effective surgery is available.

B. ACQUIRED HEART DISEASE

While great stress has been placed upon the problems of congenital heart disease in recent years, this aspect of the overall picture of heart disease will tend to return to a more minor, although fascinating, role as surgery for acquired heart disease continues to develop. The normal heart, a miniature replica, perhaps, of the visionary "perpetual motion machine," is subject daily to a variety of stresses occasioned by trauma, infection, and degenerative processes. The recognition of these states, some acute and immediately disastrous, others chronic and insidious in their development, is of paramount importance to all physicians A proper understanding and recognition of the principles at play will lead to earlier and more effectual therapeutic effort, be it medical or surgical

I. Trauma

Definition: Cardiac trauma results from any force applied either directly or indirectly to the heart and is evidenced by dissolution of tissue or its continuity, whether it be gross or microscopic Obviously, all degrees of trauma may exist either singly or in combination The etiologic agents are innumerable but, for the most part, can be grouped into two general types—crushing or penetrating

Pathophysiology: The heart, being a nonrigid organ, is able to withstand sudden, nonlacerating injuries of considerable force without impairment of its function Such an injury may be sustained to the myocardium directly, or result from force applied to the thoracic wall without fracture of ribs or external bruising. Thus, the impact of an automobile steering wheel in a traffic accident (compression between the vertebral column and thoracic cage) may cause contusion of the heart, even though no direct contact between the traumatic agent and the cardiac muscle has occurred. Similarly, the heart may be contused by blows or compression transmitted through the diaphragm A fall or blow *per se* may even cause laceration of the pericardium, of the heart and its valves, the aorta may rupture, especially should an aneurysm or some degenerative disease be present to have previously weakened the structures Acute pericarditis, auricular fibrillation, premature contractions, acute dilatation and heart block have all been said to result, on rare occasions, from violence alone.

Penetrating injuries are, as a rule, of more serious import resulting in immediate death or may be of more limited consequence, depending upon the size of the offending agent or the resultant size of the cardiac and pericardial defect. Wounds of the heart involve the right and left ventricles about equally, the atria in only seven per cent of the cases. Wounds of the thin-walled atria are more dangerous from hemorrhage than those of the ventricles; of the right ventricle more than the left ventricle, because the greater thickness of walls and greater size of the columnae carneae of

the left ventricle favor contraction and self-limiting thrombus formation. Wounds of the interventricular septum may not be as dangerous as those that open the cardiac chambers, provided the coronary arteries are not divided.

Division of the larger branches of the coronary artery produce, although not invariably, myocardial degeneration. Wounds of the auriculoventricular septum, involving the bundle of His, may be instantly fatal. Gunshot wounds are more dangerous than incised wounds; needle punctures much less serious than stab wounds. Needles may enter the pericardium or heart through the skin (paracentesis), through the esophagus (swallowed), or through the respiratory system (inhaled). Fatal puncture of the right ventricle has occurred in an attempt at sternal transfusion or biopsy of its marrow.

Bullets and other foreign bodies within the heart have provided amazing and bizarre clinical problems. They may occupy a cavity of the heart or the pulmonary artery and may even migrate as emboli along the aorta to the iliac arteries. Bacterial endocarditis, pericardial effusion, myocardial aneurysm, and cardiac rupture may be the sequelae. On the other hand, many patients harboring cardiovascular foreign bodies of this type, have remained essentially asymptomatic for many months and years following their initial injury. In Picques' case the bullet remained encysted in the pericardium for fifty-two years.

The serious consequence of cardiac wounds not immediately fatal lies in the amount of associated hemorrhage (actual and continuing) and in the development of cardiac tamponade. Marked hemorrhage after a penetrating wound of the chest indicates injury of the internal mammary artery, the heart, the great vessels, or the lung. It is rare that serious hemorrhage occurs from a wound of the pericardium alone. Thus, pathophysiologic changes vary from instant death to disability so slight that the patient continues to walk about, ultimately recovering, or dying after hours or days with the pericardium, and possibly the pleura, filled with blood.

Provided there is little or no bleeding from the visible and external wound, the immediate effect of cardiac wounds depends, to some extent, upon the size and position of the associated laceration of the pericardium. Should this laceration be large, blood will escape into the pleural space resulting in exsanguination but not tamponade. If the pericardial rent is small or becomes rapidly sealed by clot or surrounding structures the pericardial space will entrap the blood ejected from the myocardial wound with each systole. Acute compression of the heart will result, evidenced by (1) rising venous pressure; (2) falling arterial pressure; (3) a small, quiet heart (Beck's triad) (Fig. 19). The heart and vena cava being compressed, the filling of the heart is interfered with and the pressure in the venous system rises, at times reaching 16 cm. of water before death occurs. The veins are not prominent because their walls have not had time to stretch nor is the liver enlarged. The flow of blood into and out of the heart is reduced, the pulse weakens and signs of arterial failure appear. The patient is at first anxious, but later becomes unconscious from cerebral

hypoxia, while the skin is pale and cool, the cardiac sounds are distant and faint. The cardiopericardial dulness is increased, but in acute conditions the increase in size may be slight and an urgently needed operation should not be delayed to obtain a roentgenogram. Rarely, the pericardial tear may communicate with the peritoneal cavity, giving rise to the signs of peritonitis (hematoperitoneum). Rarely also, the heart may be dis-

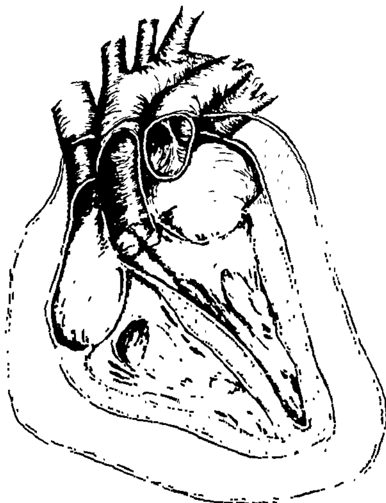


FIGURE 19. Cardiac tamponade from pericardial fluid under pressure showing compression of the ventricles but particularly of the thin-walled right atrium and venous return.

placed *into one of the pleural cavities as a result of the pericardial injury,* a condition attended by precordial pain, shock, dyspnea, and cyanosis.

Clinical Manifestations: The symptoms and signs of cardiac trauma depend upon the type and extent of the injury. Compression, contusion, and nonpenetrating injuries may produce vague symptoms and signs of weakness, irritability, and nervous instability but, as a rule, these are neither definitive or diagnostic. Their importance lies in the realization

of their possible significance, to wit—the heart has sustained a measure of damage which must not go unheeded. Appropriate supportive measures will be applied and a period of watchful awareness will ensue.

Continued and uncontained hemorrhage leading to rapid exsanguination is evidenced by initial precordial anguish, pallor, shock, marked dyspnea, rapid shallow respirations, cyanosis, falling blood pressure, weak, rapid, irregular, or imperceptible pulse, collapse, and unconsciousness. The patient may show great restlessness and anxiety, develop convulsions, repeated vomiting, involuntary dejections of urine and feces, or, from an associated wound of the lung, hemoptysis.

Acute tamponade will reveal a similar chain of symptomatic events and may be indistinguishable. Actually, the differential diagnosis is in most instances impossible, and purely academic, for both demand surgical intervention at the earliest moment possible. A gradual development of cardiac compression over a period of hours or days will lead to the more orderly and attenuated development of the symptoms, as outlined above. Great care must be taken on all occasions to look for signs of concomitant injuries to the lungs, esophagus, and abdominal viscera. Hemothorax, tension pneumothorax, rupture of abdominal organs, and injuries to the head and extremities require careful search and evaluation.

Supportive Data: Time will rarely permit evaluation of the patient by methods other than clinical appraisal. Too often the wait for laboratory data and roentgen examination has led to death, otherwise avoidable, had immediate resort to surgical measures been made. However, when time permits, the roentgenogram or fluoroscopic examination will reveal the loss of the normal cardiac silhouette and pulsation, and the presence of fluid and/or air in the pleural space. The presence of foreign bodies may be detected. There is no early perceptible electrocardiographic change; after about eighteen hours changes similar to those in coronary occlusion may appear.

Needle aspiration of the pericardial sac may be indicated if the symptoms of cardiac tamponade grow rapidly worse, but this should be done more as a therapeutic measure rather than diagnostic.

At a much later date, if and when the patient's condition has returned to normal, angiocardiography may be employed for localization of foreign bodies should their exact position be debatable by standard roentgenography alone.

Treatment: Contusions and nonpenetrating wounds of the heart will usually respond to conservative therapy. This consists of rest, avoidance of mental and physical strain, and the proper control of activity during the convalescent period, as dictated by the severity of the traumatic experience. Should an effusion in the pericardium appear, aspiration, repeatedly if necessary, should be done. It is of interest that Riolanus first recommended pericardial aspiration as a method of treatment for heart wounds in 1649. Baron Larrey relieved a heart wound by drainage in 1829. Rehn is credited with the first successful suture of a stabwound of the heart in 1896.

In recent years there has been considerable debate as to the proper management of heart wounds as seen by the average physician in non-military practice. This confusion does not exist with the patient obviously in extremis, and rapidly dying from continued and profuse hemorrhage. Such a patient demands immediate thoracic exploration with attempted

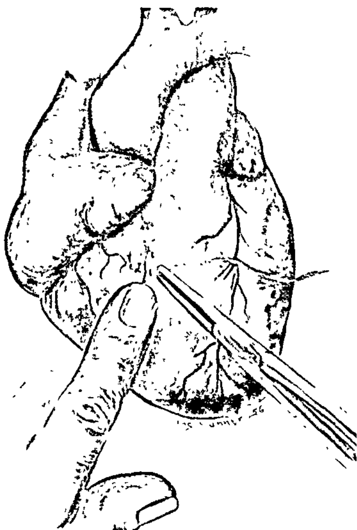


FIGURE 20 Laceration of the myocardium showing method of finger hemostasis during surgical repair by suture

control and suture of the existing wound or wounds. Simultaneous supportive transfusions, as needed, and the maintenance of an adequate airway, with high concentrations of oxygen, are essential. With this form of treatment for the patient in this condition no one can quarrel. It is rather the patient who arrives in the hospital accident ward with external evidence of a thoracic wall injury, pale, cold, conscious, or partially so; in shock, low blood pressure, rapid pulse, temporarily holding his own that

promotes the dilemma. The question under these conditions is asked repeatedly: Shall one temporize with supportive transfusions and await developments, or shall the patient be taken to the operating room immediately? The advocates for each method have strong arguments to support their school of thought and rightfully point with pride to the results obtained.

Elkin, Ravitch, and Blalock, and many others, believe that the more conservative measures will adequately care for the majority of patients. Accordingly, for the patient with a wound as described, they advise immediate infusions of blood or fluid as available. The external wound is cleansed, debrided, and closed. Should, during the period of intelligent watchful observation, the signs of cardiac tamponade appear, pericardial aspiration is performed and repeated as often as necessary to maintain an improving state. Should aspirations in this manner provide an inadequate response, or should the patient's condition rapidly and suddenly deteriorate, operative management (described below) then, and only then, becomes mandatory and is resorted to without further delay. Elkin and Campbell report eighteen cases of stabwounds of the heart of which seventeen were treated with conservative measures as outlined. The mortality rate was 5.9 per cent.

Many investigators and clinicians strongly recommend immediate surgery, maintaining that every hour lost leads to further "silent" hemorrhage, subclinical, if not obvious, deterioration, irreversible damage to sensitive tissues, such as the heart muscle and brain, and possible sepsis. Aspiration of blood from the pericardium to relieve the pressure upon the heart will often prolong life until the heart can be exposed and sutured. With or without this measure they advocate immediate exploratory thoracotomy through an intercostal incision in the left chest, evacuation of the clot in the pericardial and pleural spaces, control of the hemorrhaging myocardial laceration by digital pressure, careful suture of the myocardium (Fig. 20), partial closure of the pericardium leaving an adequate communication into the pleural space, under water-seal drainage of the pleura by catheter, and primary closure of the chest incision. High concentrations of oxygen and rapid replacement and maintenance of blood volume are essential. This form of treatment immediately instituted not only controls the primary heart lesion but allows for the early repair of other organic damage (lung, mediastinal structures, abdominal organs) and removes the danger of subsequent constrictive pericarditis and trapped lung which may result from prolonged retention of free pericardial and pleural blood and its fibrinous exudate. Maynard reports eighty-one cases of penetrating wounds of the heart with twenty deaths occurring before surgery could be performed, and of sixty-one surgically treated thirty-five patients (57.3 per cent) were salvaged.

Although the authors tend to favor the latter form of treatment, attention to the underlying principles of both methods will lead to better patient care and serve to point out that each individual case may well dictate the proper course of action.

II. Infections

Inflammatory changes of and within the pericardium are secondary to disease processes and infections carried to it by way of the blood stream or contiguously from the heart, pleura, and peritoneum. The major etiologic agents are rheumatic infections, tuberculosis, pyogenic organisms and any mechanical irritants capable of producing a transudative effusion. The advent of antibiotic therapy has greatly simplified the management of infectious processes but even so, they are recognized as passing through various acute, subacute and chronic phases. With the infection controlled the physician's major concern is that of cardiac irritation and constriction either suddenly produced or developing insidiously.

(a) Acute Pericarditis

Definition: Acute pericarditis is the rapidly progressive inflammatory reaction of the pericardium secondary to pathologic alterations within the heart and myocardium or stemming from other regions remote (*via* blood stream) or contiguous. Thus, bacterial or viral infections, hemorrhage, trauma, tumor, myocardial infarction, or chemical imbalances (uremia) may be the causative agent.

Pathophysiology: The involvement of the pericardium in various cardiac states is readily understandable. Due to its function as a closed, supportive, and protective covering, its close anatomical relationship to the heart insures its vulnerability to changes within that structure. The acute inflammatory response of any serous membrane, such as the pericardium, to disease is manifest by the effusion produced. The volume and character of the effusion will obviously effect the heart mechanically and amounts from 200 cc. upward of fluid, blood, or even air produce an ever increasing intrapericardial pressure. Depending upon the rapidity of fluid accumulation, a rising intra-auricular pressure follows due to compression of the more thinly walled atria. Such pressure leads to decreased venous return, a rising venous pressure in the peripheral veins with the eventual clinical evidence of distended veins in the neck, trunk, and extremities. In consequence, cardiac output is decreased (inadequate venous return), coronary blood flow is diminished, and arterial pressure falls.

A serofibrinous type of effusion will, in its early stages, be characterized by the presence of a friction rub ("walking in snow," "the rubbing of leather") until sufficient amounts of fluid are present to separate the epicardial and pericardial surfaces. With severe bacterial invasion a purulent pericarditis follows.

Clinical Findings: The development and type of pericardial effusion is dependent upon the underlying etiologic agent. From the onset severe and excruciating substernal and pericardial pain may be present simulating an acute coronary thrombosis. Shortly, with the increasing effusion, dyspnea, weakness, dysphagia, and profuse perspiration became prominent. These symptoms may develop even with relatively small amounts of pericardial fluid, depending upon the comparative sizes of the heart and its restraining pericardium. Increasing cardiac dulness, Beck's triad, hepatomegaly, ascites, peripheral edema, pulsus paradoxus, and consolidation

of the left lower lobe may be elicited as time passes. Fever and leukocytosis are present.

Supportive Data: Pericardiocentesis with the withdrawal of fluid will immediately confirm the diagnosis.

Fluoroscopic and roentgen examination is of great value for the demonstration of pericardial fluid. Projection in the A-P, oblique, and lateral

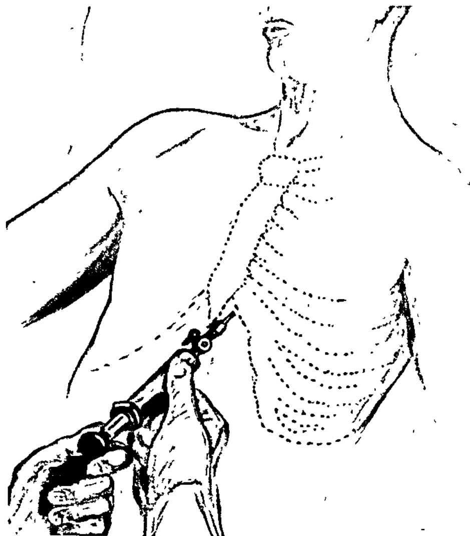


FIGURE 21. Method of removing pericardial fluid by needle aspiration.

diameters are fundamental for complete demonstration of cardiophrenic angle obliteration and cardiac displacement. The typical bulging water-bottle silhouette is diagnostic.

The electrocardiographic tracing may be quite nonspecific but inverted T waves in the classic leads, with low voltage QRS complexes are often demonstrable.

Treatment: Closed drainage of the pericardial sac by needle aspiration is the treatment of choice for the evacuation of fluid collections provided

this procedure is carried out with care. Such aspirations may be repeated as indicated without endangering the patient and may well prevent the future development of thickened, adherent, and constrictive pericardial adhesions. The antibiotics, used primarily by the parenteral route but if necessary locally, have been one of the greatest modern assets in the control of the bacterial invader. More recently, streptomycin in tuberculous pericarditis has been found to influence materially the prognosis of this condition formerly invariably fatal in the acute form.

Pericardiocentesis—aspiration through the fourth or fifth interspaces, just to the left of the sternum, is frequently used The subxiphoid route, however, is more highly recommended. This method calls for the needle insertion to be made just below and to the left of the xiphoid process with the patient's head and thorax elevated obliquely at a 35° angle. The needle is passed upward and slightly medially to enter the pericardium at its base where the position of the patient is most likely to insure the greatest accumulation of free fluid (Fig. 21).

In those cases of purulent pericarditis, or of excessively large and inaccessible serous effusions, open surgical drainage may be more advantageous. This may be carried out in the conventional manner by a small resection of the fifth left costal cartilage with direct access to the pericardium for dependent drainage. The authors prefer the approach advocated by Donaldson in which the diaphragmatic base of the pericardium is approached. By making a small oblique incision just below the xiphoid and paralleling the medial margin of the left costal arch, the left rectus sheath is divided, the rectus muscle is retracted laterally, and dissection superiorly along the transversalis fascia leads directly into the pericardium. A Penrose drain is placed to, but not into, the pericardium

(b) Chronic Constrictive Pericarditis

Definition: Chronic constrictive pericarditis, as the name implies, is a disease complex characterized by partial or complete obliteration of the pericardial space by thickened, fibrinous pericardium which has become intimately adherent to the myocardium itself thereby greatly limiting the contractive activity of the heart. Calcification may not be present but, as a rule, considerable calcium deposition has occurred either in patchy distribution or in enveloping plaques which may completely encase one or more of the cardiac chambers.

Synonyms: Chronic cardiac compression, concretio cordis, concretio pericardii, accreto pericardii, stone heart, Pick's disease.

Pathophysiology: For years there has been considerable speculation as to the etiologic factors responsible for this condition. It would appear that long-standing tuberculous infection is the commonest etiologic agent even though in many no known contact with this disease can be traced. No doubt residuals of other bacterial infections have played a role together with the fibrotic organization of unrecognized effusions and inflammatory products. Rheumatic fever and allied states have been indicted but it seems most likely that this condition produces no more than pericardial adhesions not eventuating in true constricting compression.

Two forms are said to exist—one in which the pericardium alone is thickened to leather-like consistency producing concentric compression and the other in which partial pericardial obliteration is associated with fibrous adherence to surrounding structures such as the chest wall, mediastinal structures, diaphragmatic pleura, and even the thoracic vertebra. For all practical purposes the obliterating process, as a whole, can be considered to be part and parcel of the same syndrome, for their ultimate effects are identical.

As already outlined at length under "trauma" and "acute pericarditis" the physiologic phenomenon is purely mechanical with, in this instance, the added factor of chronicity and irreversibility by conservative measures. As the thickened pericardial sac becomes more adherent and unyielding cardiac motion and excursion is increasingly diminished. Venous return is hampered, cardiac systole and diastole become limited, arterial output is lowered, and coronary flow deficient. Thus, in spite of increased cardiac effort the entire circulation becomes sluggish as clinically evidenced by venous stasis, chronic congestion of the liver, accumulation of abdominal fluid, peripheral edema, and pleural effusions, particularly on the right side.

Clinical Findings: The primary symptoms in this condition are fatigue, generalized inanition, enlargement of the liver with ascites, peripheral edema, and dyspnea (pleural effusions). Frequently the picture is almost indistinguishable from that as seen in cirrhosis of the liver, kidney disease, and cardiac decompensation from other causes, so that the true underlying causative factors are masked and overlooked. As in many another more obscure disease entity a high index of suspicion with consideration of this process in the differential diagnosis may be the lone guidepost to the recognition of the proper diagnosis The physical findings of edema, hydrothorax, hepatomegaly, splenomegaly, and the like are certainly not exclusively diagnostic without the accompanying demonstration of Beck's triad which alone may serve to direct the physician's attention to the heart.

Supportive Data: Routine laboratory studies, as a rule, are of little diagnostic significance. Serum protein studies are rarely able to account for the ascites and edema. The circulation time may be prolonged. Venous pressure measurements are usually elevated and cardiac output studies, should they be employed, show the reduction.

When considered in the light of the clinical history and findings, the fluoroscopic and roentgen examinations may often be of the greatest importance. Diminution of cardiac pulsations is strongly suggestive, but when coupled with the demonstration of calcification (often absent) of the pericardium little doubt as to the proper diagnosis remains (Fig. 22). The electrocardiogram will show little more than T wave changes and the reduced amplitude of the QRS complexes.

Cardiac catheterization and ventilatory studies are of little diagnostic value but may serve as an excellent academic measure of the overall cardiopulmonary improvement and prognosis following surgical intervention.

Treatment: It may be stated unhesitatingly that the treatment of constrictive pericarditis is surgical. Although this was recognized and a peri-

cardiectomy was performed by Hallopeau in 1910 and by both Rehn and Sauerbruch in 1913, it was not generally accepted until the past two decades. *Beck, Blalock,* and *Burwell, Heuer* and *Stewart, Harrington,* White, and Churchill, and Holman have played a prominent role in the development of our present day surgical concepts and technics.

General supportive therapy in the form of rest, high protein-low salt diet, digitalization, diuretics, and the mechanical relief of ascites and *pleural effusions by aspirations are essential in the preparation of the* patient for surgery. Such a period of preparations may be necessary for several weeks until the patient is maintained at his most satisfactory dehydrated weight. The surgical objectives are then twofold—to obtain the most adequate cardiac exposure despite the bony thorax and then, as completely *as possible, to decorticate the heart and great vessels by peri-*cardiectomy. The technic is almost as varied as the number of surgeons



FIGURE 22 Roentgenogram revealing calcification of the pericardium

performing the operation. Incision may be made through the rib cage on the left s [illegible] portions of the costal cartilages of ribs 3 [illegible] access to [illegible] the sternum horizontally, extending the incision bilaterally into the fourth interspace on either side. The authors feel that in most instances the usual *left* posterolateral *thoracic incision, carried well anterior in the* fourth or fifth interspaces (the fifth rib may be removed) will provide ready access to the performance of a most adequate pericardiectomy and will be easier on the patient (less time consuming). Only very rarely will a second operation on the right side be necessary to provide complete therapeutic relief.

The decortication of the heart is begun over the left ventricle by incising through the thickened pericardial rind down to the true epicardium which should also be removed for best results. By maintaining traction on the free edges at all times the thickened plaque can gradually be elevated

by a combination of sharp and blunt dissection. The left ventricle is usually freed before the right to avoid flooding the pulmonary vascular bed with blood unable properly to pass on into the systemic circulation because of the still intact left ventricular compression. This consideration, however, is more academic than actual in most instances. Care must be exercised to avoid injury to the superficially placed coronary vessels. Ideally, all of the constricting pericardium is removed from all four cardiac

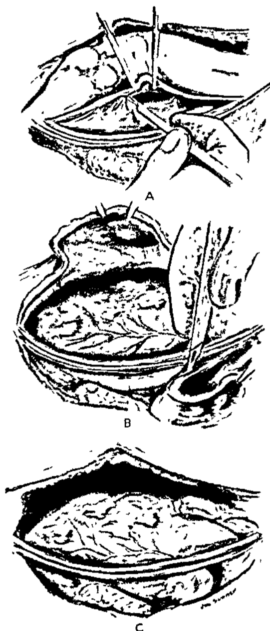


FIGURE 23. Removal of pericardium in chronic compression (constrictive) pericarditis by the left pleural approach The phrenic nerve is carefully preserved Note the imbedded calcific plaques in the myocardium left intact but with their continuity interrupted

chambers over the anterior, lateral, and inferior (apex) aspects to allow for adequate expansion and contraction throughout the cardiac cycle. Calcific deposits not infrequently are deeply imbedded in the myocardium itself and attempted removal in its entirety is not possible. Such areas are left as little isolated islands which will not interfere with a good functional result provided the continuity of the pericardial peel has been interrupted. Every *attempt to free the atrioventricular junction areas must be made* since frequently these sites, when constricted, lead to considerable vascular obstruction even though the heart otherwise be satisfactorily denuded. Inspection of the two cavae at their point of entrance into the right atrium should be made, for, again, residual constriction here may lead to continued venous stasis. The wound is closed without drainage as the chest wall is reconstructed (Fig. 23).

As of 1949, 265 operations for constrictive pericarditis were recorded in the literature. Of this group there were twenty-two deaths on the operating table and forty-eight additional deaths occurring in the early postoperative period; 118 cases were considered cured and forty-four cases improved. These statistics, of course, include the reported cases over the many years since the inception of this type of surgery, so that the results as obtained today are more highly satisfactory and the operative mortality below ten per cent.

III. Rheumatic Heart Disease—Valvular

At the present time by far the greatest field of intracardiac surgical endeavor is concerned with the problems of acquired valvular disease involving the mitral and aortic valves White has estimated that 0.5 to 1 per cent of the community at large is affected by valvular disease, particularly in those areas where rheumatic fever is endemic as in the northeastern part of the United States and northern Europe. Among the first two million American selectees between the ages of twenty-one and thirty-six in World War II, about 100,000 were found to be unfit because of cardiovascular disease and at least fifty per cent of these suffered from rheumatic valvular defects. The mitral and aortic valves are the common sites of involvement, and structural stenosis is the most serious end-result of rheumatic infection. It is little wonder, therefore, since stenosis is essentially a mechanical stricture, that surgical intervention should be considered as offering the ideal therapeutic approach provided it can be accomplished with relative safety and without the production of deleterious side effects.

(a) Mitral Stenosis

Definition: A stricture of the mitral valve in which the two anatomical leaflets become fused along their normal line of closure to eventuate in a tiny rigid slit at the mouth of the semifixed fibrotic valvular cone—the end-result of rheumatic infection.

Pathophysiology: In rheumatic disease the mitral valve develops numerous minute *inflammatory verrucae in a row along the line of closure of* the valve (Fig 24A) With continuing rheumatic activity and attempts at healing over the course of years there is a gradual development of

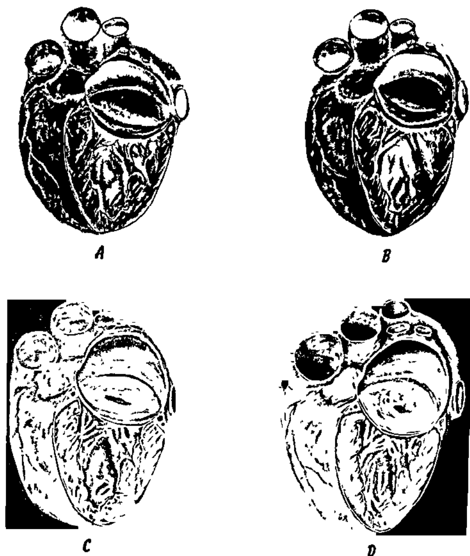


FIGURE 24 The pathological development of mitral stenosis (staged diagrammatically) A, Acute rheumatic involvement of the mitral cusp margins beaded with multiple, minute verrucae B, Early fusion of the anterior and posterior leaflets at their lateral angles (commissures) of closure C, Late mitral stenosis with fully developed, fused valve cone, well developed commissures, enlargement of the left atrium, pulmonary artery, and right ventricle by increasing vascular back pressure. Note that the left ventricle remains relatively normal in size. D, Terminal mitral stenosis with enlargement of all cardiac chambers except the left ventricle (constant congestive failure at this stage).

fibrosis, thickening and narrowing of the valve leaflets as their cusp margins become adherent at the angles (commissures) (Fig. 24B). This scarring may be limited in extent to resemble a purse-string puckering at the valve orifice with minimal involvement of the valve leaflets themselves, which remain quite pliable and of the consistency of kid glove skin. In other instances, the periorificial induration involves one-fourth to one-half of the cone leaving a correspondingly smaller margin of flexible tissue

about the base at the A-V ring (Fig. 24C). In far advanced disease the whole valve may become rigid and completely inflexible—a hard, ovoid plaque surrounding a tiny fish-mouth slit (Fig. 24D). Calcium may be present at any stage as flecks, localized infiltration, or, rarely, almost completely replacing valve tissue. Thus, as stenosis is produced, pronounced resistance to the passage of blood from the left atrium into the left ventricle ensues. Since the *egress of blood from the left atrium is impaired*, increased pressure within and considerable dilatation of this chamber results. The high intra-auricular pressure is transmitted to the entire pulmonary congestion (dyspnea), rupture of pulmonary capillaries (hemop-

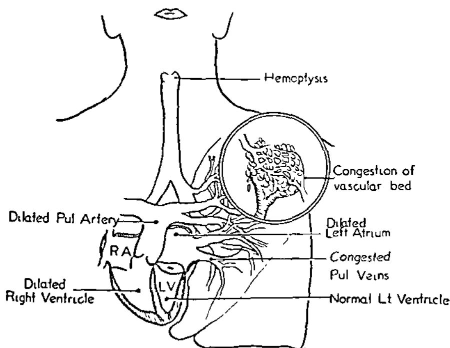


FIGURE 25 Diagrammatic representation to show the development of pulmonary vascular and right heart hypertension as a result of sustained mitral valve obstruction

chronic pulmonary hypertension results with nocturnal or exertional pulmonary congestion (dyspnea), rupture of pulmonary capillaries (hemoptysis), and failure of the right side of the heart (hepatomegaly, ascites, and peripheral edema) (Fig. 25).

Once this progressive pattern becomes heralded by the onset of fatigue and exertional dyspnea the ultimate outcome for the patient is in time invariably unfavorable. At this point the treatment by the physician will be directed toward the support of a myocardium which is vainly attempting to maintain an adequate systemic circulation in the face of an unrelenting mechanical stricture. The fort can be held temporarily but eventually under *such circumstances both the physician and the myocardium are* fighting a losing battle. It is paramount to recognize that the earliest onset of symptoms bespeaks a failing myocardial and pulmonary vascular re-

serve as the result of *already long-standing structural valvular stenosis.* To repeat, with the onset of symptoms the valvular lesion for the most part has already reached its ultimate cicatrix and progression of the patient's disability is one of symptomatic breakdown and disintegration, not of increasing structural stenosis within the valve itself. The therapeutic conclusion is obvious. The stenotic valve must be opened at the earliest suggestion of the above described obstructive phenomena if one is to avoid the inevitable progression of enlarging cardiac chambers (left atrium, right ventricle, right atrium), pulmonary edema, recurrent hemoptysis, auricular fibrillation, embolic episodes, and chronic congestive (right heart) failure.

Clinical Findings: It is important to realize that, as a rule, many years elapse between the typical attack of rheumatic fever and the development of clinically significant mitral stenosis. During the acute phase a pancarditis is present, affecting both valve and myocardium alike. In time the infiltrating inflammation of the myocardium subsides to chronicity and muscular activity continues strong, seemingly unaffected. This may likewise be true of the valves but in a considerable percentage nature's own healing and scarification processes promote contraction of the A-V ring, shortening of the chordae tendineae, hypertrophy of the papillary muscles, thickening, agglutination and calcification of the valve leaflets, and grotesque distortions of the valve aperture. In consequence, the initial systolic blow (insufficiency during the acute phase) fades to become replaced by a *diastolic rumble* eventually present throughout diastole, accentuating in presystole and terminating in the characteristically *loud and snapping mitral first sound.* The buildup of pressure within the pulmonary bed and artery gradually causes an increasing recoil in the pulmonary valve causing an accentuated *pulmonary second sound.* Thus, the auscultatory picture of pure or predominant mitral stenosis is recognized. Many variations exist, of course, but the astute clinician will recognize the inexorable development of the stenotic lesion.

During this developmental phase there may be no disability to the patient and, indeed, the insidious process may be entirely unrecognized because of the lack of any symptomatic counterpart. The ultimate victims will, in time, begin to notice undue *fatigue* and a *diminished tolerance to minimal exercise* (such as climbing a flight of stairs). This disability becomes progressive and will eventually usher in the long chain of events so commonly seen in this type of cardiopulmonary breakdown. *Hemoptysis* (rupture of pulmonary capillaries under pressure) may appear suddenly and may be the first symptom to direct attention to the underlying pathology. *Pulmonary infarction,* with its acute pleuritic picture, heart consciousness as the heart labors to provide an adequate circulation, paroxysmal bouts of atrial fibrillation, soon to become permanent, appear. With increasing pressure *orthopnea* becomes marked as do bouts of *pulmonary edema* and eventual right heart failure with its *hepatomegaly, peripheral edema,* and *ascites.* At any stage *thrombosis* within the left atrium and its appendage may develop with the ever present danger of *embolus* to the brain, visceral or peripheral arterial bed. The chain of

events is relentless and, although it may be temporarily stayed by the effectual use of rest and drugs (digitalis, mercurial diuretics, deprivation of salt, etc.) the eventual result, without mechanical, surgical correction, can only be invalidism and a shortened life span.

Supportive Data: In the early symptomatic phase of mitral stenosis, when resort to surgery should be made, roentgen and fluoroscopic findings may still be minimal. The overall cardiac size will be enlarged and the left lateral cardiac border will be straightened or will tend to be convex in the region of the pulmonary artery just below the aortic knot. Oblique and lateral projections will indicate that this enlargement is confined to the left atrium (bulging back against the barium-filled esophagus), pulmonary artery, and right ventricle. Characteristically, in pure or predominant mitral stenosis, the *left ventricle will remain normal in size*, for this chamber lies in front of the obstruction. This point cannot be too greatly stressed for it is the cornerstone of the criteria for operability. Should the left ventricle be enlarged it indicates the presence of concomitant aortic valve disease or marked mitral unsufficiency, either or both of which, if present to a marked degree, will lead to an ineffectual surgical result and oft times actually contraindicates surgical intervention. As symptoms progress the same group and type of findings persist only, naturally, to a much greater degree of enlargement.

The electrocardiogram in the early phases may remain relatively normal but as the disease complex progresses evidence of *right* ventricular hypertrophy becomes prominent. Again, the presence of left axis deviation, with its left ventricular preponderance, contraindicates surgery as it points to the fact that factors other than mitral stenosis are dynamically at play.

Catheterization of the right heart and pulmonary artery to measure the degree of hypertension in those areas gives valuable confirmatory evidence of the effect of the mitral obstruction, but the performance of this procedure is not considered essential in the evaluation of the routine patient for surgery. In questionable cases it may throw considerable light upon the exact nature of the physiologic valvular effect when the presence of mitral insufficiency is additionally suspected, and in this way aid in ruling out cases that should not be operated (characteristic pulmonary capillary curve in regurgitation). Possibly the greatest use of catheterization in this condition is its use in comparing the pressures before and after surgery as an index of success of the surgical measures from a prognostic standpoint. Pressures from 40 mm. Hg systolic to as high as 150 mm. Hg systolic in the pulmonary artery have been obtained in mitral stenosis (top normal 30 mm. Hg) and these have been observed to drop practically to normal in from six months to two years after surgery.

Surgical Considerations. ***Historical Background:*** Lest one be tempted to suspect that the surgical approach to the problem of mitral stenosis has been entirely the concept of the surgeon one has only to recall that the internist, Samways in 1898, and Brunton in 1902, was the first to propose direct surgical reconstruction of the valve. At the time of these suggestions surgery had not developed to the stage where such a bold step was considered feasible. In the years from 1923 to 1930, however,

repeated and ingenious surgical attempts were undertaken and the efforts of these pioneers, though for the most part unsuccessful, can never be forgotten even in the present era of overwhelming cardiac surgical enthusiasm. By a variety of methods designed to cut the valve leaflets or to excise a portion of the obstructing valve tissue, Allen and Graham, Cutler and Beck, and Pribram attempted to enlarge the stenotic orifice in such a way as deliberately to produce a regurgitant lesion, erroneously reasoning that by so doing the less innocuous condition of mitral insufficiency would be substituted for the highly lethal mitral stenosis.

As such surgical reasoning resulted in almost universal failure, when put into effect, the whole program of intracardiac surgery collapsed to remain in oblivion for nearly two decades. The magnitude of this fate is now made more poignant by the realization of the fact that one man, Souttar, had the answer in his grasp only to have it lost in the shuffle of the prevailing despondency. In 1925, Souttar successfully dilated a stenotic mitral valve by introducing his right index finger through the left auricular appendage and on through the stenotic orifice. He was even prepared with a small knife which could be placed alongside the finger further to cut the valve but as there was considerable regurgitation already present, cutting of the valve seemed inadvisable and dilatation alone was carried out. Souttar was impressed with the ease of the approach and with the amount and precision of the information to be gained by digital exploration. Although the operative procedure had been undertaken with the idea of cutting the anterior valve leaflet to produce regurgitation which, if carried out, would have resulted fatally, nevertheless, had the principle of "digital vision and exploration" through the appendage been more generally adopted the obvious and natural opening of the valve at the angle of its fused cusps (commissurotomy) might have been recognized years ago. This experience, however, will always remain as the model and precursor to the present successful application of mitral valve surgery.

In the mid 1940's, surgical attempts to relieve mitral stenosis were revived. In 1946, Bailey repeated the Souttar operation and although the patient died two days later, postmortem examination revealed that the stenotic valve had been partially split at the commissures producing enlargement of the orifice while at the same time maintaining valvular competence. In 1947, Smithy and Harken, still accepting the theory that the production of insufficiency was unavoidable, persisted in their attempts to resect valve tissue, albeit in smaller sections than those resected by Cutler years before. This revived procedure was referred to by Harken as "valvuloplasty" and embodied the production of "selective insufficiency."

In 1948 Bailey, Glover, and O'Neill performed the first successful, planned division of the commissures of a stenotic mitral valve, a procedure now known throughout the world as commissurotomy, the name given it by Durant. Since that day over 5000 commissurotomies have been performed in this country and abroad with uniformly good results to amply justify its widespread acceptance.

Technic: With the patient lying on his right side in the true lateral position, a left posterolateral periscapular incision is made and carried

from the vertebral column well anteriorly just under the breast. The pleura is entered through the fourth interspace and the lung, which is usually congested, thickened, and somewhat rubbery in texture (long standing capillary congestion) is retracted posteriorly. The pericardium is opened vertically, posterior and parallel to the phrenic nerve to expose amply the left atrium and its appendage. A gross estimate of individual chamber size of the right and left ventricles, left atrium, and pulmonary artery can be made. The left ventricle will be found to be relatively normal in size and a distinct diastolic thrill can be felt over its apex. The other chambers and vessels are invariably enlarged from 1 to 4 plus, depending upon the duration and severity of the disease. The base of the appendage is pursestringed with heavy braided silk by incorporating small bites of epicardium preferably in the atrial wall itself. The base of the appendage is gently clamped by a specially devised instrument for the purpose, and an opening is made near the tip of the appendage. The clamp is momentarily opened to allow outward bleeding to wash out any loose thrombotic material which may be present. Further dissection with removal of thrombi may be necessary but that which is firmly attached to the appendageal myocardium is left intact. The right index finger is inserted into the appendage as the clamp is removed and the purse-string drawn taut, about the finger, thus insuring minimal bleeding. The finger is well tolerated within the left atrium and can remain there for exploratory and manipulative purposes for many minutes, provided the circulating flow of blood is not more than momentarily impeded. The entire interior of the atrium can be rapidly explored by passing the finger over the atrial septum, into the orifices of the pulmonary veins, and over the valve itself. Occasionally, mural thrombotic material can be detected which, of course, is left undisturbed. The character of the valvular tissue can be readily appreciated and the size and location of the mitral orifice immediately determined. The cusp margins are, as a rule, thickened and rolled by fibrotic induration and in almost fifty per cent of the cases will be the seat of some calcification from mere flecks to partial or complete encirclement. Rarely, the calcification may involve most of the leaflet tissue itself, but usually is localized to only one area, the anterior or aortic leaflet, the point nearest the left ventricular outflow tract being the most commonly involved Fibrosis and thickening of the leaflets may be minimal to extreme, in which case the entire valve cone may be fixed and rigid. As a rule, however, considerable pliability remains circumferentially about the base of the valve (kid glove skin or thin shoe leather texture), despite the periorificial cicatrix, which will allow some restoration of valvular motion once the leaflets have been separated at the commissures. The valve leaflets themselves must not be cut or split for lethal insufficiency will be produced, as amply shown in years gone by. If by gentle finger pressure on the anterolateral commissure, it can be made to split in the proper place and direction, this commissure may be opened completely to the myocardial wall This maneuver can be accomplished more frequently when the valve is greatly thickened or calcified, for there is less damage under these circumstances of splitting in the wrong place. It is preferable in most instances—always when the leaflets

are relatively thin and pliable—to slide a guillotine knife into the atrium alongside the finger and accurately place the hook and blades directly on the commissure and cut across the fused rind at the commissure. This will avoid undue trauma and pressure being applied to the valve and will



FIGURE 26. Method of mitral commissurotomy with right index finger and guillotine knife inserted through the left auricular appendage and placed to divide the anterolateral commissure Insert depicts the valvular opening after commissurotomy

prevent tearing or avulsion of the valve leaflets. Once the separation has been started by the knife and the tough lip traversed, the remainder of the separation can be carried out by further finger pressure until the myocardial wall has been reached. Should another thickened and unyielding area be encountered the knife is readily available for an additional incision.

In this manner the original contracted orifice (cigarette size or smaller) can be opened to the width of two fingers (normal three fingers) and such an opening will insure a highly satisfactory functional result (Fig. 26) If this size cannot be reached a similar cut is made on the posteromedial commissure, incising just across the fused rim but not far back into pliable valve lest undue regurgitation be produced in this more vulnerable site. Anterolateral division, alone, is adequate in most instances and the beginner should be very wary about tampering with the posteromedial commissure. Frequently, by passing the finger through the opened valve, subvalvular manipulation will free the fixed and agglutinated chordae tendineae to allow for better valve action. The degree of jet-like regurgitation (if any) present before and after commissurotomy can easily be appreciated by holding the finger at the mitral orifice. Experience will dictate the degree of regurgitation that can be tolerated by the patient if such is inadvertently produced or increased

The finger and knife are withdrawn, the purse-string suture tightened and tied, the isolated tip amputated for pathologic study, and the remainder is oversewn for additional hemostasis. The operative field is flushed with warm saline, all debris and clots removed from the pericardial sac which is then partially closed only to allow drainage into the pleural space. The lung is expanded, the pleura drained by catheter and the chest wall closed in the usual manner. Operating time in the average case will be 1 to 1½ hours, skin to skin. A minimum of fluid and blood is given throughout surgery to guard against overloading the pulmonary circuit. Modern anesthesia using pentothal, curarelike substances and intravenous 0.2 per cent procaine, as needed, will allow the patient to be awake in the operating room as the dressings are applied. A check of peripheral vessels is carried out and motion in the extremities is sought to rule out the presence of central or peripheral embolization. The use of temporary occlusion of the carotid vessels to prevent cerebral emboli during valvular manipulation, as recently described, is dangerous and ill-advised for emboli may occur anyway and the risk of injury to the carotid arteries with additional cerebral anoxia makes this maneuver more hazardous than worthwhile

Classification of Patients with Mitral Stenosis: For a thorough appreciation of the stages through which the patient with mitral stenosis may pass a classification has been prepared in an effort to combine a functional and therapeutic yardstick for evaluation of the patient for surgery.

Stages of Mitral Stenosis

I. Asymptomatic
II Statically incapacitating
III Progressively incapacitating
IV. Terminally incapacitating
V Irreversible

Stage I includes patients with the auscultatory findings of mitral stenosis but who as yet have no symptoms. Patients in *Stage II* have progressed to the point where symptoms under physical activity have developed, but

the patient, living within his own limitations, remains on an even plateau. *Stage III*, the largest group and one encompassing many variables, includes those who, despite the best medical therapy, are losing ground. *Stage IV*, terminally incapacitating, includes those patients in whom there is constant evidence of congestive failure even with limited physical activity. Most of these can be rendered relatively free of their accumulating tissue fluid only by the strictest of medical regimens. A certain small percentage of those in this group will ultimately prove after surgery to have been in *Stage V* and to have had irreversible changes. As yet, it has been impossible routinely to separate patients in these two stages by clinical and physiologic methods; hence, we reserve stage five to classify those whose condition, despite a technically adequate commissurotomy, remains relatively unchanged.

Indications for Commissurotomy: In the light of the foregoing discussion, the selection of patients for surgical intervention can be simply stated. The ideal candidate is the patient with pure mitral stenosis and beginning symptoms of cardiopulmonary dysfunction such as shortness of breath upon exertion. Fatigue out of all proportion to the patient's physical activity is frequently a prodromal or accompanying finding. At the moment the mere presence of a well defined mitral diastolic murmur without accompanying symptoms is regarded by many as insufficient reason to suggest surgery. Possibly the day will come in the future when such a thought will seem unreasonable.

All other indications for commissurotomy are merely compromises from the ideal but for years to come an understanding of the more advanced but altogether salvable states is essential. An outline under seven major categories will most succinctly serve this purpose:

1. History.
   a. Early cardiopulmonary dysfunction—ideal.
   b. Marked dyspnea, hemoptysis, reversible failure—acceptable.
2. Age· Elastic range—physiologic rather than chronological
   Oldest case to date—age sixty-two.
3. Valvular defect
   a. Pure mitral stenosis—ideal.
   b. Associated mitral insufficiency and/or aortic valve lesion in presence of normal left ventricle—acceptable.
4. Roentgen findings
   a. Left atrium and right ventricle minimally enlarged—ideal
   b. Minimal left ventricle enlargement—questionable but acceptable
5. Electrocardiogram.
   a. Normal electrical axis or right ventricular strain—ideal.
   b. Left axis shift—never acceptable.
   c. Auricular fibrillation with controllable ventricular response—acceptable
6. Functional capacity.
   a. Stage II (statically incapacitating)—ideal.
   b. Stage III (progressively incapacitating)—acceptable.
   c. Stage IV and V (debatable)—occasional good result.

7. Complicating factors
   a. Arterial embolic episodes
   b. Recurrent hemoptysis
   c. Hypertension (?).
   } Acceptable, and may be urgent
8 Contraindications.
   a. Acute rheumatic fever.
   b. Subacute bacterial endocarditis until controlled.
   c Associated marked mitral insufficiency or aortic lesions with all cardiac chambers enlarged.

Results of Commissurotomy: The authors have performed some 1000 mitral commissurotomies over a period of eight years. These cases have been subjected to critical analysis from both the surgical and medical standpoint. Sufficient time has now elapsed in the majority of these cases to warrant certain conclusions—seventy-five per cent of all patients, regardless of the stage of their disease, have been very definitely improved and two-thirds of these can be described as being excellent. Excellent means that the patient has been restored to a normal, productive life, enjoying normal activities without obvious limitation Low salt diet and mercurial diuretics are no longer necessary. Some are still taking a small daily maintenance dose of digitalis as a precautionary measure.

Those patients with improvement (not regarded as excellent) have returned to an almost normal life and activity within their own particular limitations, determined on a trial and error basis Most of this group are under medication because of the demands of their more greatly enlarged sphere of activity. A few, terminally incapacitated, have now become so amenable to therapy that reasonable activity requires digitalization only. The range of improvement in this group varies widely with the condition of the valve found at surgery and the degree to which valve function could be restored. Their progressive downhill course has been abruptly terminated or reversed, some to regain a high level of efficiency and others to remain on an improved plateau.

Fifteen per cent have been essentially unimproved due primarily to the presence of multivalvular disease and significant degrees of mitral insufficiency.

The overall operative mortality from the inception of this program to the present time has been six per cent. Cases in Stages II and III have an even lower mortality rate (3.5 per cent) but are balanced to the level of six per cent by cases in Stages IV and V. No patients in Stage I have been subjected to surgery. The remaining five per cent of patients have been late deaths primarily in those cases in Stages IV and V who were found to have irreversible cardiovalvular and pulmonary, hepatic or renal vascular changes which no mere relief of mechanical obstruction could be expected to alter.

(b) Mitral Insufficiency

Definition: Mitral insufficiency (incompetence, regurgitation) is a state of mechanical derangement of the mitral valve in which its leaflets are unable to accomplish closure of the atrioventricular orifice during ventricular systole. It is most commonly the result of rheumatic heart disease

but can be present as a result of cardiac enlargement associated with other entities such as hypertension, aortic insufficiency or stenosis.

Pathologic Anatomy and Physiology: It has long been the belief that mitral stenosis and insufficiency were always present in combination; that neither could occur as a "pure" lesion. The advent of intracardiac surgery has revealed that this is not necessarily so. Numerous cases of "pure" lesions of both varieties have been encountered by the surgeon It is true, however, that in the majority of cases of predominant mitral stenosis there is some degree of insufficiency. On the other hand in predominant or massive mitral regurgitation there is less frequently a stenotic element. It should be clear that when one of these lesions is dynamically significant, the other is practically never so. Obviously, if the orifice is so small that it causes hemodynamic changes of obstruction, it is not large enough to permit significant regurgitation. Conversely, if the orifice is incapable of closing in systole to allow significant regurgitation, it cannot be small enough in diastole to cause significant obstructive derangement. It is necessary, then, to think of these two types of lesions as separately "pure" or predominant according to the manifestations and the hemodynamic findings.

In the study of the pathological anatomy of regurgitant lesions of the cardiac valves, inspection of the opened postmortem specimen is extremely inadequate. Experience with digital exploration of the valve in the living heart, at surgery, and with the use of methods for the reproduction of cardiac hydrodynamics in the intact postmortem heart has clarified many aspects of the pathologic anatomy and mechanics of this lesion.

Three principal factors determine the incompetence of the mitral valve. The degree to which each contributes is variable. Usually, the major factor is the enlargement of the mitral annulus. The other important factor is the loss of valvular occluding tissue (or area). The third is that of immobilization or restriction of the leaflet by tension due to shortening of chordae tendineae and also to the annular enlargement.

The inflammatory lesions of rheumatic valvulitis lead to a process of healing characterized by marked scarring, thickening, shortening, and distortion of the valve leaflets and chordae tendineae. If extensive degrees of commissural fusion fail to occur then the shortened leaflets are rendered incapable of coaptation. This leads to the early state of the regurgitant lesion. Here, the regurgitation is due to the *absolute loss* of valvular occluding substance. The regurgitant defect demands dilatation of the left ventricle to accommodate the residual blood volume above that necessary to maintain adequate cardiac output. The regurgitant blood volume and rise in left atrial pressure lead to enlargement of this chamber as well Increased volume of both left heart chambers results in an enlargement of the atrioventricular annulus This annular dilatation increases the discrepancy between the areas of valvular occluding elements available and the orifice which is to be occluded. This additional discrepancy can be described as a *relative loss* of valvular occluding substance. As the ring enlarges and the relative discrepancy becomes greater, the magnitude of the regurgitating volume increases and perpetuates a vicious cycle of

progressive aggravation of regurgitation and enlargement of the annulus.

The development of a state of massive mitral regurgitation is associated with two mechanisms which produce profound alterations in the circulatory dynamics. One acts upon the pulmonary circulation, the right heart, and the venous system in a manner not unlike that of the obstructive lesion of mitral stenosis. This is due to the progressive increase in regurgitated volume which by increasing the left atrial pressure represents, in effect, a physiologic or functional obstruction to blood flow. This phenomenon is further enhanced as left ventricular action reaches the limits of tolerance in handling a vastly increased load, in terms of blood volume The second mechanism affects the systemic and coronary circulations. As the size of the regurgitant orifice increases, ventricular ejection *via* the aortic valve decreases. Left ventricular output is delivered to the zone of least resistance. One can think of the two orifices of the left ventricle as competing for its output. In the normal state, complete closure of the mitral valve offers unyielding resistance and thus ejection is all *via* the aortic valve. The loss of mitral valvular occluding substance decreases the resistance and thus some of the ventricular output is delivered to the atrium. Systemic blood flow will remain adequate only as long as the resistance offered by the mitral valve in systole is significantly greater than that opposed by the aortic valve and peripheral vasculature. When this critical limit is reached, ventricular ejection *via* the aortic valve will deteriorate It will do so progressively as the incompetent mitral orifice increases in size. Circulatory failure under such circumstances is due to low cardiac output or forward failure. The overload on the left ventricle plus the depletion of its coronary blood supply by the decreased output and the increased left atrial mean pressure will also determine a state of congestive or backward failure.

Clinical Findings: The patient with mitral insufficiency, like those with stenosis, has generally had a recognized attack of rheumatic fever some years before symptoms of circulatory derangement become apparent. One has the impression, however, that this course is shorter than that of the individual with stenosis. Once symptoms appear, the evolution of the condition is considerably more rapid than that of mitral stenosis. It resembles the course of the patient with aortic stenosis The earliest symptom is that of fatigue. Weakness and "air hunger" are prominent shortly thereafter. The dyspnea or air hunger is unlike that of mitral stenosis There is less importance attached to it by the patient Hemoptysis is a very rare and late occurrence. Palpitations are complained of frequently but again differ from the sensation due primarily to atrial fibrillation experienced in stenosis. This arrhythmia is frequent but the patient complains primarily of the increased forcefulness of the pulsation. In the later stage the patient will give a history more like that of congestive failure with dyspnea, orthopnea, edema, and ascites. Cough and hemoptysis may occcur. Angina pectoris is occasionally experienced. Arterial embolic phenomena are rare

The physical examination will reveal characteristically an enlarged heart, a loud harsh prolonged systolic murmur which may be continuous with a muffled first mitral sound The murmur is best heard at the apex and radiates laterally to the axilla and medially and upwards toward the base

of the heart. Not infrequently the murmur is quite prominent over the aortic valve area and may even be transmitted to the neck. The greatest caution must be used in interpreting the murmur of advanced mitral insufficiency which can be very easily confused with that of aortic stenosis. The pulmonic second sound will frequently be accentuated. The pulse will be, most often, irregular and shallow. The blood pressure will be in the low normal ranges or may even be under 100 mm. Hg systolic in the advanced stages. Late in the course of the process signs of congestive failure will become evident. These will develop rapidly and will respond poorly to the usual medical regimen.

The roentgenogram of the chest will show marked enlargement of the heart. The largest hearts which we have seen were in patients with massive, pure-mitral insufficiency. The left atrium and the left ventricle will be the most prominent chambers. The atrium, indeed, frequently reaches aneurysmal proportions. The degree of right sided enlargement and of pulmonary vascular engorgement noted will also depend on the stage of the disease.

The electrocardiogram will show left or combined ventricular strain or hypertrophy. Atrial fibrillation is very common. Bigeminal pulse is also frequent, especially in the advanced stages. Occasionally variable degrees of heart block may be seen.

Cardiac catheterization, both right and left, provides the most accurate means of establishing a diagnosis in the, not uncommon, case in which there is strong clinical suspicion of associated aortic valvular disease. The right heart pressures will be elevated. In the earlier stages right atrial pressure will be normal and pulmonary artery pressure may be only mildly elevated. In the late stages pulmonary artery pressure may be markedly elevated, sometimes as high as 100 mm. Hg systolic or more. The pulmonary wedge pressure will also be high. Frequently the contour of the pulmonary wedge pressure tracing will be characteristic of the lesion. Peak pressure in the left atrium will be quite high, 25 to 80 mm. Hg systolic, however, the minimum left atrial pressure will be normal or only mildly elevated. The left atrial pressure pulse contour is pathognomonic. The left ventricular and aortic pressures will be in the low normal range or occasionally below 100 mm. Hg systolic. Ventricular end-diastolic pressure is normal or may be elevated in the advanced stages. The left ventricular pressure pulse curve shows an asymmetrical decline which begins early in the ejection phase. There will be no significant diastolic gradient across the mitral valve, or systolic gradient across the aortic. Oxygen content of mixed venous blood may be normal or low. Arterial oxygen content will usually be normal. The cardiac output will be moderately to markedly diminished.

The angiocardiogram will demonstrate massive enlargement of the left atrium with persistence of dye in this chamber.

Surgical Considerations: The efforts of many surgeons and investigators to devise a means for correcting mitral insufficiency have resulted in a large number of suggestions, many revealing the ingenuity and resourcefulness

of the proponent. The early experiments of Murray and of Templeton and Gibbon attempted to implant pericardium or vein grafts to replace valve leaflets. Bailey, Glover, and O'Neill reported the use of pericardial slings placed subvalvularly across the orifice to act as flap-valves. Glover and Henderson showed these to be useless in view of the degenerative changes which occurred in the transplanted tissue. Harken used numerous types of baffles implanted in or about the orifice. Bailey and associates, more recently, described technics in which the valve leaflets were sutured with pericardium or in which baffles or plugs of cartilage covered with pericardium were suspended within the lumen of the heart to act as additional occluding material. Numerous other workers have suggested different types of prosthetic valves, tissue implants, or technics for invagination of appendage or atrial walls. All of these efforts have been based on the premise of increasing the amount or of replacing the valvular occluding elements. None of these methods has been successful Some have been used clinically in significant numbers of patients without substantial effect. No objective evidence that relief of the regurgitation was achieved by these methods has been reported.

In view of the fact that replacement of valvular occluding substances seemed the most difficult approach to the problem, Davila, Mattson, Glover, and co-workers undertook to re-evaluate the pathologic and anatomic aspects of the situation. The significance of the annular enlargement was realized early in the course of these studies which began in 1952. The results of this work were published in 1954, suggesting that perhaps the more promising approach to the correction of mitral regurgitation lay in developing methods for reducing the size of the ring. This is to say that rather than to attempt to increase the size of the "stopper" to fit the orifice, it seemed more logical to attempt to reduce the size of the orifice to fit the "stopper" In this manner all available valvular occluding material could best be used. Among such early efforts were those of O'Neill and Glover which included the plication of imbrication of pericardium about the left atrium and the injection of sclerosing agents in the atrioventricular groove in the hope that fibrosis would reduce the size of the annulus. In the laboratory Davila, Glover, and associates developed a surgical technic for the placement of a circumferential suture, or "purse-string," around the mitral ring. This procedure was studied in detail in experimental animals It was shown objectively that artificially produced mitral insufficiency could be consistently corrected without the production of mitral stenosis nor of any other deleterious effect upon the heart when the perfected technic was properly performed. The procedure was first used clinically in a woman with massive, pure mitral regurgitation in January 1955. Tracings of left atrial pressure pulse taken at surgery, phonocardiograms postoperatively, and subsequent x-rays demonstrated for the first time the correction of this lesion in a patient. This patient is living today, one and one-half years after the operation, is employed full time as a seamstress and leads a comfortable and useful life Subsequent clinical experience in twenty-seven patients to date has repeatedly demonstrated

the mechanical efficacy of the method. Several other workers, notably Hilario, Borrie, Hurwit, Kay, and Nichols have suggested or tried modified technics based on the same principle.

At the present time, it appears that the concept of reduction in the size of the annulus is sound. Even if open heart surgery of the mitral valve becomes safe and practicable, this principle may well remain the most logical unless and until it becomes possible to replace completely the diseased valve with a satisfactory prosthetic. The latter achievement does not seem likely in the foreseeable future.

In the normal mitral valve the annulus is a rather subtle structure. It is simply the base of the valve leaflets at the atrioventricular groove. This circumferential structure limits the size of the atrioventricular orifice. The thin, pliable, and extremely mobile leaflets are capable of retracting during diastole so that the atrioventricular communication during this phase is almost equal to that of the circle bounded by the annulus. If one were to excise the entire valve leaflets, at their attachment, the resulting orifice would be but a little larger than the orifice present during diastole at maximal retraction of the leaflets. The latter can be termed the *effective orifice* since it is that through which atrioventricular blood flow occurs in diastole. The orifice limited by the annulus can be termed the *potential orifice* since it would be that resulting in the case of complete absence of valve leaflets. In the diseased mitral valve the potential orifice enlarges, sometimes to an enormous size. However, fibrosis of the leaflets and minimal degrees of commissural fusion prevent the effective orifice from enlarging in equal proportion. It is this fact that permits and, indeed, indicates the use of the "mitral purse-string" to reduce the size of the potential orifice without encroaching upon the effective orifice. Complete encirclement of the mitral annulus offers the additional feature of stabilizing the size of the ring and thus preventing progressive enlargement with the associated aggravation of regurgitation. Cinematographic demonstrations of the mechanics of this principle with the use of the pulse duplicator* have confirmed its efficacy.

The surgical technic employed consists of the placement of a circumferential cotton tape (umbilical tape) around the mitral ring (Fig. 27). A special needle is passed initially from the posterior aspect of the heart, beneath the coronary sinus and from a point just to the left of the posterior descending coronary vessels into the periannular fat pad, through the posterior base of the interatrial septum and into the lumen of the right atrium. The needle point is then guided along the right side of the septum, forward, to emerge in the transverse sinus at the junction of the anterior atrial walls in the anterior base of the septum. This part of the procedure is performed with digital, intracardiac guidance using the operators left index finger in the left atrium. The needle is then threaded with the tape which is drawn backwards to emerge posteriorly at the initial entry-point of the needle. The anterior tail of the suture, after covering a segment of

[illegible] which makes possible the reproduction of [illegible] circuit incorporating a postmortem heart [illegible]



FIGURE 27 Diagrammatic representation showing position of the circumferential suture (mitral purse-string) before being tied.

it with a pericardial sleeve to prevent erosion at the base of the left atrial appendage, is passed beneath the circumflex coronary artery to emerge anteriorly from the periannular fat pad, just to the left of the anterior descending coronary vessels. The posterior tail of the suture is stitched forward into the atrioventricular groove in the periannular fat underpassing the lateral descending branches of the circumflex coronary artery. The two tails come together and are tied in front of the heart, a few millimeters to the left of the origin of the anterior descending coronary

artery. The suture is tied while the operator controls the degree of constriction by the intracardiac palpation of the annulus, the effective orifice, and the regurgitant jet. Tracings of the atrial, left ventricular and aortic pressure pulses indicate the degree to which relief of mitral regurgitation has been accomplished (Fig. 28).

Results of Mitral "Purse-string": To date twenty-seven patients have been subjected to this operation. It was decided in planning the course of the experimental development of the procedure, that its initial application in patients would be limited to twenty-five or thirty cases in advanced stages of the disease in which medical therapy had no further benefits to offer. The twenty-seven patients operated so far were all in a state comparable to the Stage IV in mitral stenosis cases. That is, they were in congestive failure and totally incapacitated physically. Fourteen of these

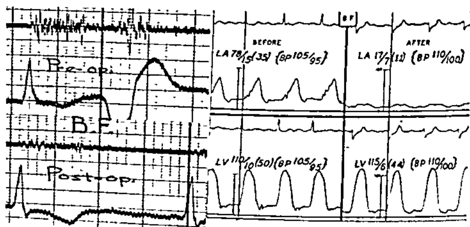


FIGURE 28 Left, pre- and postoperative phonocardiogram. Right, pre- and postoperative left atrial and left ventricular pressure pulses Note the change in contour as well as in pressure. The S-T segment depression seen in the electrocardiogram tracings during this recording was transient.

cases were actually intractable by medical means. Despite prolonged confinement to bed and a rigorous medical regimen, they could not be brought out of the state of cardiac decompensation. Thirteen patients were also in congestive failure but by confinement to bed in the hospital and by energetic medical therapy their congestive state could be improved or compensated. These two groups are considered separately.

Of the group of fourteen intractable cases seven were operative deaths. Two of these had uncorrectable lesions. One had resulted from a "finger fracture" of a stenosed mitral valve performed elsewhere, which instead of opening the commissure caused a laceration of the aortic leaflet of the mitral valve which produced a massive regurgitation. At postmortem it was concluded that this lesion could not have been corrected by any currently known means. The other patient had sustained an almost total destruction of valve leaflets by the disease process. Essentially no useful valve elements remained. One patient died in ventricular fibrillation which ensued prior to the beginning of the placement of the "purse-string." Two others have died of uncontrollable hemorrhage resulting from dissection

in the transverse sinus. These had been explored previously and there was an extensive adhesive pericarditis which obliterated the usual anatomic space and landmarks. The state of the other two was simply not compatible with tolerance of a surgical procedure. Six of these patients survived the operation and lived from one to ten months postoperatively. In all of these, hemodynamic and other studies showed satisfactory or even dramatic correction of the regurgitant lesion. These patients showed variable degrees of transitory improvement only to deteriorate again and die. Autopsy examinations were performed in all but one of these cases. The findings consisted of extensive changes of chronic congestive failure in lungs, liver, and other tissues. The heart was generally enormous. The ventricular myocardium was dilated and hypertrophied, pale and soft. There was no indication of coronary occlusion attributable to the operation. The "purse-string" was well situated in every instance and the corrective effect persisted. This was demonstrated, in some of these specimens, on the pulse duplicator. One patient of this group is living today, four months after surgery, in a much improved state.

The reasons for the outcome in the case of the survivors of this group can be the subject of much speculation There is reason to believe that correction of mitral regurgitation after left ventricular failure has been present for some time may add to, rather than decrease, the load upon the ventricular muscle. Many aspects of the problem require much more understanding of the pathological physiology of mitral insufficiency than is available today before they can be adequately explained.

Of the group of thirteen patients in whom medical therapy in the hospital afforded some degree of improvement, three have been operative deaths. One of these resulted from the administration of 500 cc. of totally incompatible blood during the operation. One died three days postoperatively in a state of shock. The question of terminal heart block was suggested by a bradycardia which appeared in the final moments of life. An electrocardiogram, unfortunately, was not obtained. The third patient died three months postoperatively as the result of subacute bacterial endocarditis due to infected thrombosis upon a portion of the suture which had inadvertently been introduced into the left atrium. This was the only serious technical error in the series. The remaining ten patients have lived for periods of three to eighteen months. All have shown remarkable improvement in their physical, subjective, and objective status. Some of the earlier patients have returned to full employment or full-time housework. Several have shown significant decrease in heart size on x-ray examination from sixteen days to one year postoperatively. In the two patients which have now been observed for about eighteen months this decrease in heart size has persisted.

The encouraging results in this latter group of patients indicates that the procedure is successful when used in properly selected cases. Actually none of these subjects has been, even remotely, an ideal candidate for surgery. The survivors represent a salvage of forty per cent in a group whose prognosis was otherwise uniformly poor. Further observation of these cases and the use of the operation in better candidates will determine,

in the future, the true place of this procedure. Four statements can now be made, however, and substantiated with objective evidence for the first time: Mitral regurgitation can be mechanically relieved by circumferential suture of the mitral ring. This operation is effective in the majority of cases of this lesion, even in the presence of calcification or of variable degrees of stenosis. Reduction in the size of the mitral annulus to significantly decrease regurgitation is not associated with production of mitral stenosis. An immediate improvement in the state of most cases has been attained and has persisted in the less advanced patients for as long as one and one-half years.

(c) Aortic Stenosis

Definition: A stricture of the aortic valve in which the three anatomical cusps become fused along their normal line of closure to eventuate in a tiny, rigid, triangular opening at the mouth of the semifixed fibrotic valve cone—the end-result of rheumatic infection and possibly of atherosclerotic vascular disease.

Pathophysiology: As in all valvular pathology, the changes noted vary according to the duration and severity of the underlying etiologic agent be it rheumatic or, upon occasion, arteriosclerotic. Multiple, minute verrucae line the cusp margins during the early course of rheumatic involvement. With progression, fusion of the cusp margins appears from the cusp bases in toward the lumen of the valve orifice. All varieties of distortion may thus occur depending upon the degree of fusion within the three commissures. The cusp margins become thickened, rolled, and eburnated. Contrary to the average finding in mitral stenosis, cases of aortic stenosis tend to develop calcification within the cusps at a very early stage leading to greater rigidity of the obstructing diaphragm and less pliability to the valve leaflets. With loss of flexibility the valve tends to remain in a fixed position and varying degrees of insufficiency frequently result. As a rule, however, some degree of motion is retained at the base of the valve leaflets which, although greatly thickened, move as does stiffened shoe leather.

The physiologic disturbances to such an obstruction within the main outflow tract of the left ventricle are obvious. Each ventricular contraction provides a slow ejection of blood as a jet into the aorta. Because of the constant and unyielding valvular barrier the cardiac output becomes fixed and cannot be increased readily upon demand such as is the case in the normal heart. Thus, in time, overexertion and eventually even slight exertion, increasing the need for additional circulation, leads to an inadequate vascular circulation causing anoxia (dizziness and fainting). The systolic blood pressure is, therefore, not high but its peak level is sustained over a longer interval. The diastolic pressure becomes elevated with a consequent decrease in the pulse pressure.

Coronary blood flow becomes reduced, not only by the diminished volume of blood, but also by these pressure changes as described. Concomitantly, the left ventricular musculature becomes greatly hypertrophied (Fig. 29). This increased muscle mass, caused by overwork, makes even

greater than normal demands upon the coronary circulation, thereby increasing the relative inadequacy and disproportion of the coronary flow. It is little wonder, therefore, that such patients experience symptoms of coronary disease (anginal pain, substernal oppression) even though no

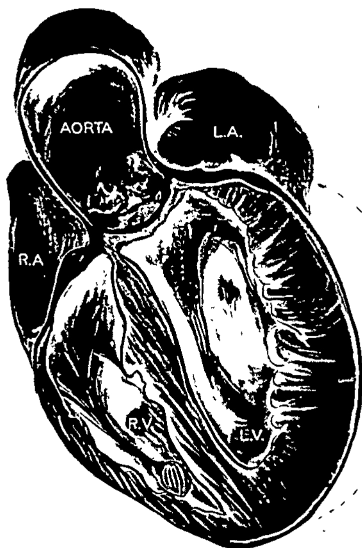


FIGURE 29 Diagrammatic representation showing advanced aortic stenosis with valvular calcification, post-stenotic dilatation, and hypertrophy of the left ventricle

actual pathologic change can be demonstrated within the coronary tree.

Eventually the left ventricle shows signs of failure at which time dyspnea, pulmonary congestion and generalized fluid retention may develop. When this occurs the patient is in serious straits and his downhill course progresses rapidly.

Clinical Findings: Whereas mitral stenosis is seen predominantly in females, aortic stenosis is most often present in males. Minor degrees of aortic stenosis may exist for years without the production of significant disability, as is true of other similar valvular states. However, with increasing stenosis, the patient becomes progressively disabled as his cardiac stroke output diminishes. As stated above, symptoms of cerebral anoxia and coronary insufficiency may be the earliest manifestations of the severity of the valvular process. Surgical correction must be considered at this time for further delay results in additional deterioration of the myocardium. Dyspnea and signs of congestive failure appear relatively late and bespeak of almost irreversible myocardial damage. Indeed, because the left ventricle plays such a major role in the maintenance of the systemic circulation, once it fails the patient's prognosis is grave and a fatal outcome is near. In this respect aortic stenosis is somewhat different from mitral stenosis for, in the latter condition, signs of failure can be tolerated for long periods of time because the left ventricle remains an effective, relatively normal chamber. In aortic stenosis, however, the major chamber (left ventricle) after failure has developed, may be worn out and cardiac recoil is less apt to occur even should the valvular obstruction be effectively relieved. Thus, early resort to aortic commissurotomy is imperative.

Physical examination, in addition to the previously mentioned pulse and blood pressure changes, reveals an enlarged heart (primarily left ventricle) with a loud, rough, systolic murmur heard maximally just to the left of the sternum in the third interspace, somewhat widely transmitted. A thrill is usually palpable, the pulse most frequently regular.

Supportive Data: As in all cardiac disease, the importance of radiologic examination is becoming more widely appreciated. Fluoroscopic and roentgen evaluation in various projections will demonstrate a heart enlarged to the left, primarily the increased size of the left ventricle. The other cardiac chambers may show little change unless heart failure is present or there is associated multivalvular disease. Actually, the outside diameter of the left ventricle may remain almost normal for a considerable period of time, for the hypertrophy in aortic stenosis is concentric (increased inward thickness of the myocardium with diminution of lumen of the left ventricle). As the effects of aortic stenosis become more prolonged, dilatation as well as hypertrophy is present and then obvious chamber enlargement becomes more readily apparent (lateral projection shows the ventricle to project posteriorly overlapping the thoracic vertebrae). The aortic arch becomes prominent, particularly its ascending portion due to the post-stenotic dilatation occasioned by the constant jet of blood through the diminutive aortic valvular orifice.

The electrocardiogram will demonstrate the presence of left ventricular hypertrophy and myocardial damage.

Cardiac catheterization and angiocardiography are of little value as a diagnostic aid in this condition.

Surgical Considerations: Tuffier, in 1941, attempted to dilate the aortic ring of a young man suffering from aortic stenosis by invaginating the wall of the aorta with his forefinger, thrusting it into the stenosis

without opening the aortic wall. This is the first recorded attempt to relieve this condition by surgical means. The patient is reported to have been living and improved ten years later. Little came of this noteworthy effort and contribution until recent years. Smithy, in 1947, and Bailey, Glover, and O'Neill shortly thereafter have worked extensively on the problem, both in the laboratory and clinically. Attempts to divide the valve with sharp



FIGURE 30 Aortic stenosis with its method of surgical correction diagrammatically portrayed The aortic dilator is inserted through the left ventricular *myocardium near its apex and directed through the aortic valve*

hooks and knives, both through the aortic wall and up through the left ventricle produced so much valvular insufficiency that this method was obviously impractical. Further experiments to sidetrack the left ventricular blood into the aorta using autogenous aortic grafts and prostheses to bypass the aortic valve failed. Success was finally achieved by introducing a specially devised dilating instrument which, when placed upward from the left ventricle through the strictured aortic orifice, satisfactorily divides one or two (never three) of the aortic commissures, thus releasing the cusps from their state of fixation and allowing for a measure of restored valve action.

Briefly, the operative approach called for a left anterolateral thoracotomy, the introductions of the dilating instrument through a relatively avascular area of the left ventricle near its apex and lateral to the left descending coronary artery. The dilator is directed through the valve. By compression of the grip handle, the dilating head opens to split dilate one or two of the fused commissures (Fig. 30). The best of such instruments is the two bladed dilator as proposed by Brock.

This operation by the technic described, or by one of its earlier adaptations, has been performed throughout the country in perhaps 500 cases. In the earlier experimental stages the mortality was high but with the present refinements, as described, has dropped to below ten per cent. It is, therefore, now safe to state that a technic is at hand which offers great relief to patients heretofore doomed to an early demise.

The results in those cases of pure aortic stenosis operated upon to date have been highly satisfactory, relief of symptoms has been dramatic, and the initial improvement has been maintained to the time this is written (oldest case now followed for four years). It has, in recent months been possible to relieve both aortic and mitral stenosis existing in the same patient by performing mitral and aortic commissurotomies at the same operation. A number of satisfactory results have been obtained in this manner, provided significant insufficiency was not present in either valve at the time of surgery.

(d) Aortic Insufficiency

One of the most difficult of all valvular lesions to correct or modify by surgical means is aortic insufficiency. To date (1956) no completely successful method is available but strides to this end have been made. Slings using pericardium or pliable plastics passed through the root of the aorta just distal to the valve to act as flapping plugs, have not been satisfactory. No evaluation of the authors' method of injecting sclerosing solutions about the external surface of the aortic valve to promote circumferential contraction and thus provide approximation of the valve leaflets can be given at this time. More recent efforts to apply externally a purse-string suture for circumferential constriction of the aortic ring similar to mitral purse-string have not been satisfactory. In a beautifully controlled series of experiments over a period of several years, Hufnagel has shown that the experimental animal can tolerate indefinitely the insertion of a "plastic valve" into the aorta distal to the origin of the left subclavian artery (Fig.

31). This valve consists of a highly polished and durable tube of plexiglas in the lumen of which a small, round ball rides back and forth in response to the pulsatile flow of the blood stream. Such a prosthesis has been employed by him and others in human aortic insufficiency in some 300 cases with encouraging results. While at best a prosthetic valve placed in the



FIGURE 31 Prosthetic valve (Hufnagel) shown in position.

descending thoracic aorta can only control the regurgitant hemodynamic effect below the valve (some seventy per cent relief of left ventricular overwork) *it is felt that in* many desperate instances this may well be worthwhile for symptomatic relief and to prolong life more comfortably. Admittedly, however, this prosthetic valve is not the final answer but represents an ingenious step in the right direction.

IV. Tumor of the Heart

Although neoplastic disease plays a very major role in the field of surgery as a whole it has received little attention in the surgery of the heart and vascular system. This is understandable when one considers that cardiac new growths are rather uncommon and, when present, are usually metastatic in origin, a part of rather widespread malignant dissemination Primarily, tumors of the heart, however, have been reported in sufficient numbers to warrant certain conclusions even though in years gone by and even at present they have rarely been diagnosed antemortem.

Benign tumors are much commoner than malignant growths. Of these, myxomas arising in the endocardium of the left atrium from the interatrial septum are most frequent. Fibromata, lipomata, leiomyomata, hemangiomata, and lymphangiomata have all been described. The malignant lesions, rare as they are, are of the sarcoma variety. They occur most commonly in the right heart arising from the atrium, interauricular septum, or pericardium.

Cardiac tumors present great diagnostic problems. Most often there are no signs or symptoms to telegraph their presence. A tumor should be suspected, however, under certain circumstances, as suggested by Pfeiffer: Unexplained or atypical, sudden, progressive treatment-refractory congestive failure especially in a young person; unexplained or atypical alterations in cardiac rate or rhythm; unexplained obstructions to cardiac blood flow such as valvular stenoses without the usual antecedent history of progressive valvular changes and sudden death without previous cardiac symptomatology all are suggestive. The authors have seen two cases of simulated mitral stenosis caused by myxomas arising from the left interatrial septum near the mitral valve. These tumors are frequently partially pedunculated, soft, gelatinous structures which can be milked down into the mitral orifice during cardiac contraction, giving rise to the typical symptoms and findings of mitral stenosis. These tumors might have been diagnosed before surgical exploration had greater attention been paid to the preoperative history that changes in the patient's position accentuated the cardiac symptoms and signs. In favorable instances tumors of this type might be successfully removed through the left auricular appendage by grasping them in a strong suction tip while the pedicled base is gently disengaged. The danger of producing an embolus, of course, is ever present but such a method might be feasible after the manner employed by neurosurgeons for the removal of certain brain tumors.

The successful removal of benign lesions of the heart has been reported by Beck who, in two instances, has removed cystic lesions from the external myocardium of the ventricles.

The authors have had occasion to excise a lemon-size aneurysm of the left ventricle which was partially filled with whorls of thrombotic material. The presence of this mass had been noted (unchanging golf ball size) for some five years but recent rapid enlargement suggested the necessity for surgical intervention. The diagnosis of an intramural tumor was considered preoperatively, although the probable presence of the aneurysm found at surgery was considered most likely.

Obviously this field of endeavor will never play a large part in surgery of the heart but it is reasonable to suspect that a number of successful surgical resections of tumors on or within the heart will be reported as *greater diagnostic effort and acumen is applied to cardiac disease.*

V. Coronary Artery Disease

Definition: Coronary artery disease is the commonest type of all heart disease. Normal aging processes and pathological degenerative disease causes narrowing of the arterial lumen of the coronary vessels This progressive narrowing leads to a reduction in oxygenated blood supply to the myocardium. At first there may be relative myocardial ischemia (greater oxygen demand than supply) with cardiac pain on effort (angina pectoris); later there may be occlusion of the vessels with varying degrees of myocardial infarction. The amount of damage depends upon the caliber of the vessel and the area of the heart supplied as well as to the extent of development of collateral circulation distal to the occlusion. There is sudden death, in approximately twenty per cent, due to ventricular fibrillation. Cardiac decompensation develops in about twenty-five per cent as the heart gradually fails in its duties as a pump The infarcted myocardium heals by fibrosis in many patients and may leave them with variable degrees of restriction in activity Cardiac deaths occur ultimately, however, in ninety-five per cent of patients who have experienced coronary occlusion.

Pathophysiology: Coronary sclerosis and thrombosis occur mainly in the first three or four centimeters of the coronary arteries with progressively less sclerosis peripherally. For this reason, when vascular obstruction takes place the area of myocardial infarction may be large unless *intercoronary* arterial anastomoses are present to allow for a retrograde supply of oxygenated blood Therefore, survival from coronary artery occlusion depends upon the degree of *intercoronary communications* In normal young hearts it has been shown that far less than ten per cent have such anastomoses. Thus, it is firmly established that, functionally at least, the coronary arteries are end-arteries Under various stimuli anastomoses will develop to compensate for relative insufficiency of oxygen. Relative insufficiency may originate in the blood itself (anemia), in the aeration of blood (pulmonary disease), in the myocardium (hypertrophy), in the endocardium (valvular disease), or in the coronary arteries themselves (coronary atherosclerosis).

These facts account for the poor prognosis of coronary occlusion in the younger age group and the better outlook when the gradual changes of aging or the other stimuli mentioned above have been present to promote collateral circulation over the years.

Clinical Findings: The clinical picture of coronary insufficiency is that of angina pectoris with substernal pain described as choking, strangling, or vise-like compression, especially that initiated by physical (possibly emotional) effort of some type. The pain may radiate to the shoulder and arm, *especially to the left Coronary occlusion usually manifests itself by* severe anginal pain, nausea, vomiting, collapse, shock, fever, arrhythmias, friction rub, drop in blood pressure, and signs of left heart failure.

Supportive Data: Coronary insufficiency, even of considerable degree, may or may not be evident on the electrocardiogram. By placing stress on the heart as by the Master two-step exercise test typical changes may be elicited.

Coronary occlusion will show leukocytosis, rapid sedimentation rate, reduced vital capacity, prolonged circulation time, and electrocardiogram changes. These electrocardiogram patterns are usually characterized by RS-T elevations progressing to deeply inverted T waves, large Q waves, and reciprocal relationship between leads 1 and 3.

Surgical Technic: The surgical attack on the effects of coronary artery disease has been directed toward the relief of cardiac pain and toward improvement of the inadequate blood supply of the heart occasioned by the fact that the coronary arteries are functionally end-arteries with poor collateral cross-circulation.

Angina pectoris can be surgically relieved by cervical and upper thoracic sympathectomy or alcohol injection of these sympathetic ganglia. Total thyroidectomy has been employed to reduce the patient's basal metabolic level (oxygen demand) to within the range of available blood flow (oxygen supply) through his diseased arteries.

Revascularization of the heart has been approached by the following methods: (1) Vascularization through the cardiac surface by adhesions, granulomas, and direct vessel grafts; (2) arterialization of the coronary venous system; (3) establishment of intercoronary anastomoses.

To evaluate these operations certain criteria must be established as the "tests of benefit." In the human, improvement can be subjectively recognized by decrease in angina, and objectively by their ability to tolerate increased work loads without electrocardiographic or clinical evidence of coronary insufficiency. In the dog, more drastic tests can be applied, such as, ligation of a major coronary artery. One established test, the ligation of the descending ramus of the left coronary artery at its origin, results in a seventy per cent mortality in normal dogs, the remainder surviving despite severe infarction. This ligation causes myocardial anoxia to the muscle supplied by the artery with resulting infarction and variable degrees of interference with the conduction system causing ventricular fibrillation and sudden death.

Extracoronary vascularization has been used by Beck, O'Shaughnessy, Rienhoff, Thompson, and others by attaching grafts of muscle, fat, pericardium, lung, or omentum to the surface of the heart, or by producing adhesions and granulomas through the use of mechanical and chemical irritants or inflammatory agents. Vineberg implants the internal mammary artery into the myocardium. In dogs with such extracoronary anastomoses, Beck reports approximately a fifty per cent reduction in the normal mortality after ligation of the descending ramus of the left coronary artery. Results in humans have shown promise by relief of pain and increase in work tolerance in some cases. Careful evaluation will take many years.

Arterialization of the coronary venous system has been accomplished by Beck by the insertion of a blood vessel graft between the aorta and coro-

nary sinus or by direct aortic-coronary sinus anastomosis. Thus, oxygenated blood from the aorta is shunted into the coronary sinus which normally collects venous blood from the heart and drains into the right auricle. At a second stage of the operation the coronary sinus is almost completely obstructed (to 3 to 4 mm.) where it empties into the right auricle and thereby diverts the fresh blood from the graft back into the coronary venous system. Thus, the great network of veins becomes functionally arteries. Because of accessory venous channels in the heart (thebesian system), venous blood then drains directly into the cardiac chambers. This operation benefits the ischemic heart by a vast retrograde supply of oxygenated blood which has been shown experimentally to pass backward through the capillary bed into the damaged area. Later benefits result from the development of intercoronary anastomoses so produced. Experimentally, dogs will now tolerate ligation of the descending ramus of the left coronary artery with practically no mortality (eight per cent) or minimal infarction. The operation is being applied to humans with angina pectoris and coronary occlusion. When the graft has remained patent there has been marked subjective and objective improvement. If the graft has thrombosed, at the second stage of operation, sinus ligation and asbestos powder irritation will produce favorable improvement in many people. Later evaluation of this technic has shown that while improved myocardial oxygenation results initially, in due time the venous bed becomes thrombosed thus negating the hoped for clinical improvement by this form of therapy. This operation has been abandoned, at least temporarily, in favor of the less innocuous operation of pericardial poudrage employing finely powdered asbestos as the irritating substance applied to the myocardium within the pericardium. The rationale obviously is the promotion of intercoronary anastomoses by bridging the patent portions of the major coronary vessels with highly vascular inflammatory reaction. The possibility of further improving myocardial vascularity by promoting anastomotic channels from the pericardium and other adjacent tissues of course is ever present. The entire process can be enhanced by simultaneous partial ligation of the coronary sinus which increases to some degree the pressure within the coronary venous bed presumably opening an optimum number of vascular channels for improved oxygenation.

Innumerable patients have been subjectly improved by some such modification of pericardial poudrage and initial statistics would suggest that definite inroads have been made in the relentless mortality rate which has placed coronary artery disease at the head of the list among the killers of mankind.

C. CARDIAC STANDSTILL

Synonyms: Cardiac arrest, cardiac asystole, cardiac slowdown, cardiac stoppage.

Pathophysiological Considerations: Gradual or sudden cessation of cardiac contractions is not uncommon during periods of circulatory stress. It is seen during the induction of anesthesia, at the time of an endotracheal catheterization or bronchoscopy, with abrupt alterations in the patient's

position following major surgical operations, during shock, hemorrhage, intrathoracic manipulations, and intra-abdominal mesenteric traction. It is also seen associated with hypoxia, coronary occlusion, air embolism, intravenous drug administrations, and in certain other medical illnesses. It is believed by many that cardiac standstill is usually due to vagal inhibition of cardiac contractions and is referred to as the vagovagal reflex. Many authorities refute this belief. It is our thought that such a reflex does exist, but only as a supplementary and contributing factor. More often the standstill primarily owes its existence to *poor cardiorespiratory function (anoxia)* and that additional insults to such impaired mechanism will make the heart susceptible to these reflexes. Shock and exsanguination may be, in their own right, sole contributing factors.

Cardiac arrest appears to be an ill-chosen term, since the implication is that heartbeats cease without warning. More often this is not so, as experiences at open chest operations will bear out. There is a warning period in which the contractions become either slow or weak. In all probability this is usually unnoticed until the heart has completely stopped. Since cardiac standstills occur under many circumstances, such as drownings, violent accidents, electrocutions, carbon monoxide poisonings, and severe illnesses which most often occur at some distance from hospital care, it is impossible that we will ever successfully treat the majority of these cases. When ventricular fibrillation is associated, as often it is in electrocution accidents, the chance of successful resuscitation becomes almost nonexistent. There is no real excuse, however, for not treating such a development when it occurs in the operating room where all necessary facilities are available. It is quite probable that the majority of hospitalized cases could have been prevented with a somewhat closer observation of the patient, and prompt, early treatment.

Treatment, Prophylactic and Definitive: It is to be realized that surgical procedures have been extended to accept more "bad risk" cases, therefore, the incidence of cardiac standstill in the operating room should be increasingly greater. In operating upon such border-line cases it is essential to make a careful preoperative evaluation of the patient and anticipate accordingly. Adequate management of fluid therapy and replacement of blood loss during surgery is imperative. Prevention of hypoxia and asphyxia from any cause is of *paramount importance*. This obliges careful attendance to adequate evacuation of tracheobronchial secretions and the maintenance of maximal respiratory exchange at all times. Surgery should be performed as gently as possible while making all efforts to avoid traction procedures. At times, when such procedures are unavoidable, constant attention should be directed toward the heart action. Atropine sulfate, 0.6 to 1.2 mg. (1/100 to 1/50 grain, should be administered promptly when bradycardia is noted. This usually increases the rate and forcefulness of the contractions within thirty seconds. When the heart ceases beating the patient will display a peculiar pale-grey color, or somewhat mottled cyanotic appearance. The pupils become completely dilated and do not react. All the while, the patient usually continues to make respiratory efforts for some minutes, which serve only to mislead

those in attendance and prevent realization that the time for action is at hand. For this reason we have come to employ the following plan of action.

When, during induction, the anesthetist cannot obtain satisfactory blood pressure readings, or radial pulse, he immediately feels for the carotid pulsations. Failing to detect such pulsations, he announces this fact to the operating team without hesitation. The surgeon will immediately make an incision in the left chest along a line corresponding with the third, fourth, fifth, or sixth rib (any one of these will do in the emergency). We have never yet encountered active chest wall bleeding in any case where carotid pulsations were unobtainable. The intercostal muscles are divided with the scalpel and the pleural space is entered Of course, during this time the anesthetist is applying positive pressure through the

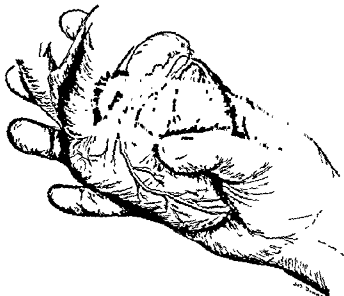


FIGURE 32 Method of performing rhythmic cardiac compression during standstill of the heart

anesthesia machine, *via* endotracheal tube, using only pure oxygen. The pericardial sac is palpated and the heart will be motionless or, at best, show very feeble and ineffective beats. Without delay, the heart is squeezed or compressed with the fingers of one hand in such a manner as to force out the blood from the ventricles (Fig 32). The grasp is rhythmically released to allow filling, and the heart is again wrung out This cyclic performance is carried out at a rate of nearly sixty per minute In the meantime intravenous transfusion is instituted and when satisfactorily running, an intra-atrial transfusion may be started. This latter type of administration has the advantage of rapidly raising the blood pressure in the aorta without the danger of overloading the venous circuit. If the heart does not respond well within a minute or two it is best to open the pericardium in order to have better control of the compression movements. The one-hand technic can be used, or if the heart is slow to respond, the two-hand technic can be utilized, since this can be continued longer

without fatigue. When the beat becomes rhythmical, but is still weak and does not pick up in strength, it will be helpful to inject the chamber of the left ventricle with adrenalin solution (1:1000). Usually 1 cc. is sufficient. Once the beat becomes strong and regular it will usually continue indefinitely so long as the factors that caused the original standstill are not in operation (such as anoxia, blood loss, vagus nerve stimulation, visceral traction, and drug overdose). The success of the procedure depends largely upon the speed with which action is taken. The two key areas that suffer first from lack of circulation are the brain, and the heart itself. Deprivation

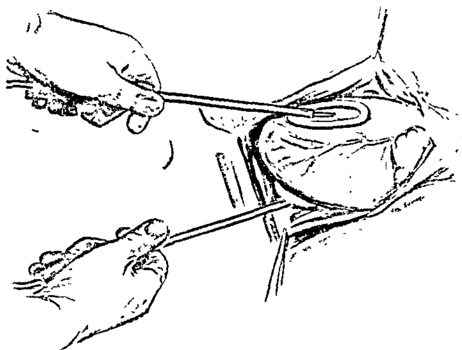


FIGURE 33 Position of electrodes in performing electric shock used in defibrillation—diagrammatically portrayed

of oxygen for periods of over five minutes usually results in permanent and irreversible damage to these structures so that death is certain. For this reason we hasten to engage in this procedure with no strict regard for sterile technic. Infection has been no serious problem in those that have recovered.

Ventricular fibrillation: The most serious immediate complication of cardiac standstill is the fearsome event of fibrillation of the ventricular musculature.

Such incoordinate contractions of isolated groups of muscle fibers fail completely to bring about emptying of the ventricles. Efforts to restore normal cardiac action by manual compression will always fail so long as the fibrillation persists. Obviously then, it is essential to treat this complication immediately.

To this end a number of surgeons have utilized electric shock of suitable character in an effort to induce a simultaneous refractory phase in the

muscle fibers, so that with recovery, all elements will again revert to simultaneous coordinated contractions (Fig. 33). Recent reports relate numerous successes in this direction

At times cardiac action will resume without further aid, but more often it will be necessary to persist with manual compression before the desired response is realized.

A varying degree of emphasis is placed upon the value of certain drugs designed to assist or strengthen the heart muscle. Greater experience alone will supply the precise answer. Adrenalin and other closely related drugs are of certain value in stimulating the myocardium immediately and directly, but carry the objection of also causing hyperexcitability which may, indeed, lead to ventricular fibrillation Injectable digitalis is often used and, in full therapeutic doses, may be of value. Kay and Blalock recommend $CaCl_2$ in ten per cent solution for injection into the left ventricular cavity, believing it to possess the accelerator stimulation of epinephrine hydrochloride, as well as, the muscular stimulation of digitalis.

While the above procedures do not contribute directly to definitive heart surgery, they, nevertheless, provide a wider margin of safety during the course of heart operations and in our experiences to date it has meant the difference between success and failure in a number of instances

D. EXTRACORPOREAL CIRCULATION AND CORPORAL HYPOTHERMIA

The surgical dictum that exposure is the first requirement for the accomplishment of satisfactory operative procedures has been the basis for the numerous and recently fruitful investigations leading to the development of methods for open heart surgery. Cardiovascular surgery has evolved first from procedures performed upon the great vessels, then, intracardiac methods applicable in the closed heart without interruption of the circulation. The logical progression has led to the application of two principal methods which have now been successfully employed to open the heart

Corporal Hypothermia: The demonstration by numerous investigators that cooling of tissue is associated with significant reduction in their demand for oxygen is the basis for the use of hypothermia in cardiac surgery. The time necessary for the performance of most corrective procedures on intracardiac defects is quite short In the normothermic individual, the brain will tolerate an hypoxia state, equivalent to total circulatory interruption, of no more than five minutes. The aim has been then, to increase the length of time during which the circulation can be stopped by decreasing the oxygen demand of the brain and other organs. Extension of the time limit can be partly accomplished by cooling the subject to 10° or 20° below the normal.

Bigelow's pioneering efforts led Lewis and Swan to develop technics of surface cooling which have been used clinically by them and numerous other surgeons to repair certain congenital lesions successfully and with a large degree of safety. There are, however, many limitations to this approach to open heart surgery

The profound physiologic changes induced by hypothermia have been the subject of studies carried on by numerous investigators. Only a limited amount of practical knowledge has been established. The high incidence of ventricular fibrillation in the cooled state and the appearance of certain phenomena in the post-hypothermia period have not been amenable to satisfactory control.

Total circulatory occlusion can be relatively safely accomplished for periods of as much as twenty minutes. This has made possible opening of the right atrium and the pulmonary artery for the repair of interatrial septal defects and valvular pulmonic stenosis. Since these lesions can be successfully corrected by safer, closed methods, this limits the applicability of hypothermia in present day cardiac surgery. Recently, the aortic valve has been approached by opening the ascending aorta under venous occlusion in the hypothermic patient by Lewis, Morrow, and others. This accomplishment may be significant in view of the difficulties encountered in aortic valve surgery by closed methods. The high incidence of ventricular fibrillation associated with ventriculotomy in the cooled state makes the method unacceptable for surgery within the ventricles. Thus it is not applicable to the correction of some of the commonest lesions, namely, interventricular septal defects and tetralogy of Fallot. Aortic occlusion for resection and replacement of vascular segments has been aided by hypothermia.

The use of surface cooling by Bigelow and many other surgeons, including the authors, in conjunction with closed heart surgery in cyanotic infants or in severely advanced valvular disease, appears to increase the margin of safety in operating on such cases.

Introduction of the principle of hibernation by Laborit and the French workers has merited numerous studies of the possibilities of ganglioplegic drugs used in conjunction with physically induced hypothermia. There is some experimental evidence indicating that this approach may lead to improvement in this work.

Further systematic studies on the effects and on the control of hypothermia will undoubtedly assign it its due place in the armamentarium of cardiovascular surgery.

Extracorporeal Circulation: The [illegible] has been the dream of many for a long time. [illegible] cessful use of a pump oxygenator [illegible] technic an interatrial septal defect has opened the way to the dramatic advances which have been made in 1955 and 1956.

The continuing efforts of Gibbon, Jongbloed, Mustard, Dennis, Crafoord and Bjork, Kolff, Helmsworth, Golan, Melrose, and many others set the ground work upon which the success of Lillehei and his associates at Minneapolis and of Kirklin and his group at The Mayo Clinic is founded.

The requirements of an extracorporeal circulation are simply two: it must be capable of providing for gas exchange with blood, and it must drive the circulation by withdrawing venous blood and returning it at suitable pressure and in suitable volume to maintain life during the re-

quired period of time. Thus the apparatus must consist of two basic parts —an oxygenator and a pump.

The problem of oxygenating blood has been approached from many aspects. It is primarily a mechanical problem of exposing a sufficient amount of blood to an atmosphere of oxygen in a period of time which will permit the maintenance of satisfactory blood flow. The smaller the amount of blood exposed, the more rapidly and completely it will become saturated with oxygen and give off carbon dioxide. Thus it becomes a matter of spreading blood thinly to expose the greatest possible amount to the gas. Blood can be oxygenated rapidly by bubbling oxygen through it. This, however, may be associated with foaming. Oxygen can also be introduced into the blood across a membrane permeable to the gas but not to fluids. Thus apparatus for oxygenating blood, employing filming, bubbling, or a membrane interphase, have been built and evaluated. Most of these will provide satisfactory oxygenation and CO_2 elimination The crucial features must be a suitable capacity to handle adequate blood flows, a minimum of dead space, and a minimum of trauma to cellular elements of blood. Simplicity of construction and maintenance are additional desirable features.

The pumps must be capable of handling large enough volumes, must be free from sources of contamination of the blood, and must deliver the necessary flow to maintain acceptable circulatory pressure with minimal trauma to the formed elements of the blood These requirements can be met by a variety of pumps. The most satisfactory are those which employ the principle of compression and synchronized valving of the intact tubing which carries the blood. The DeBakey, Melrose, and Sigmamotor pumps are the outstanding examples.

A very few years ago despite the success of Gibbon in one case, there was a general feeling of disappointment and a lack of enthusiasm concerning the future of extracorporeal circulation. The success of closed heart surgery and the promise of improvement in the use of hypothermia temporarily shifted interest along these lines. The realization by the Minneapolis workers led by Lillehei of the possible significance of the "azygos flow" concept proposed by Andreasen led to their eventual use of crossed circulation. This method employed an adult human being as an extracorporeal heart-lung machine to sustain the circulation of an infant subjected to open heart surgery. The observation that experimental animals could survive blood flows as low as that supplied by the azygos system alone appears to have been the determining factor in leading to the spectacular success of crossed circulation. This procedure was cumbersome and, more significantly, subjected a normal human being to certain risks. It established, however, the feasibility of maintaining life in small subjects for adequate periods of time with flows as low as twenty or thirty per cent of normal.

Since that time, in about two years, there has been a renewed and vigorous attack on the problems of total cardiac bypass Notable among the current workers in this field are Kirklin, Lillehei and DeWall *et al.*, and Effler and Kolff. These men and others have successfully used various

types of apparatus. The major achievements have been attained in the correction of interventricular septal defects. In this lesion the mortality has been reasonable and the results have been remarkable. Numerous other congenital anomalies have also been corrected by these means. Among these lesions are common atrioventricular canal, tetralogy of Fallot, pure infundibular pulmonic stenosis, and atrial septal defects.

The recent demonstrations of the possibility of achieving cardiac standstill induced by potassium citrate during bypass and the use of retrograde perfusion of the coronary sinus as a means of maintaining the coronary circulation promise the development of methods for performing open surgery on the left heart structures, thus, more satisfactory aortic valve surgery seems within reach in the near future.

The rather abrupt jump, however, of extracorporeal circulation from the trial and error stage of the past to its very empirical, though largely successful applications of today has left a large gap in our knowledge and understanding of the physiologic and metabolic derangements occasioned by the still existing functional limitations of these technics. This hiatus must be filled before open heart surgery can become universally applicable. This will only be done in time through the systematic study of the numerous factors which play a role in the performance of these procedures. Some of the points which need urgent clarification are concerned with more complete and better controlled studies on blood flow requirements; on the significance of alteration of blood by its passage through the artificial circulation; on the precise limitations of metabolic changes compatible with survival; on the role or possible use of hypothermia, cardiac standstill, retrograde coronary perfusion, ganglioplegic, vaso-oppressor and other drugs as adjuncts to bypass. The clarification of these and other incomplete areas of understanding can lead to refinements in the apparatus and perfection of its controlled use in the near future.

The achievement of universally applicable open heart surgery will make possible the complete correction of most congenital defects. It will also make possible some improvements in valvular surgery. This is particularly so in the case of the aortic valve. It must be borne in mind, however, that in dealing with valvular lesions there is relatively little that can be done to improve the results of closed surgery in mitral, tricuspid or pulmonic stenosis, short of valvular replacement. In mitral insufficiency, the principle of annular reduction will probably remain the major one just as the concept of commissurotomy will in stenosis. There is considerable evidence that plastic procedures performed on valve leaflets, which involve significant injury to the corresponding tissues, will be unsatisfactory due to the healing and scarring processes to which these structures are prone. By providing better access to it, the aortic valve will be amenable to more satisfactory operations, primarily as regards stenosis. Restoration of valvular function will remain dependent upon the state of the diseased valve until satisfactory artificial valves can be constructed and implanted in place of the diseased one. Another aspect for possible future development with the aid of extracorporeal circulation may be that of coronary disease. Replacement of segments of coronary arteries is not beyond the realm of possibility.

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EDGAR V. ALLEN, M.D.
AND
EDGAR A. HINES, JR., M.D

24

Normal Blood Pressure and Its Physiologic Variations

Introduction: In spite of a large amount of work which has already been done on blood pressure, there is still great need for information in regard to standards of normal and physiologic variations from normal.

As so often happens in medicine, when physicians first discovered hypertension, they immediately devoted most of their efforts to curing it, and but few attempts were made to determine when a given pressure represents disease and when it is only a physiologic variation from the average. Even today there is great need for a more careful biometric and anthropologic approach to the problem.

The records made in the early years are of little value today, because they were made with all sorts of instruments and with methods different from those which are now commonly used. Fortunately, with the passage of time, a considerable degree of standardization has been achieved, both as regards the instrument and the method. Today practically everyone uses a cuff of standard width and a manometer which is calibrated in terms of millimeters of mercury. For careful scientific work, the mercury instrument is to be preferred, because there must always be a little fear that an aneroid type of manometer is out of adjustment

In the early days, blood pressures were taken by the palpatory method, but in more recent years most observers have been listening for the sounds and have been getting readings about 5 mm. higher than those obtained by palpation. Even today, when studying diastolic pressures, the statistician must be careful to learn what method was used in determining the end point. Most observers take as a criterion of the diastolic pressure the beginning of the fourth Korotkov sound.

But even when two observers are using standard instruments and the same technic in measurement, they tend to differ markedly in their readings, and this for a number of reasons. Some measure carelessly; they allow the column of mercury to drop rapidly, and they read to the nearest multiple of ten on the scale. Others have unusually acute or unusually poor hearing, and this makes a difference. But even when the oscillations of the manometer are recorded graphically, as they are with the Erlanger and the Tycos instruments, there is still much likelihood of differences of opinion, as was shown by Kilgore[36] many years ago. He sent duplicate sets of records obtained with an Erlanger instrument to a number of the leading physiologists and cardiologists in the United States; he asked them to

Pioneers in the Advance of the Knowledge of Diseases of the Heart by the Aid of Instruments of Precision



[illegible]
destined to become the only contribution to the subject for 100 years



Bowditch, in 1871, established the first physiological laboratory in America and made the initial investigation of the "all or nothing" principle of contraction in heart muscle



Einthoven made possible the development of modern electrocardiography by the introduction of the delicate string galvanometer for measuring the cardiac action currents of Waller The records he obtained of the heartbeat he named "electrocardiograms."



Sir Thomas Lewis, developing the method of electrocardiography in the present century, has succeeded in bringing complete order out of the chaotic state of our knowledge of the cardiac arrhythmias



Mackenzie perfected and used the polygraph in the study of the arrhythmias and was the first to make simultaneous records of the arterial and venous pulses His pulse tracings, examples of skill and patience led him close to the solution of all of the cardiac irregularities

mark points of systolic and diastolic pressure, and he received conflicting reports. For further discussion of some of these problems, the student should turn to papers by Judson and Nicholson,[47] MacWilliam,[62] Norris, Bazett, and MacMillan,[72] Schrumpf and Zabel,[78] and Warfield.[93]

Carelessness, of course, is one of the greatest causes of obtaining poor results, and the statistician will always want to know how and by whom the records under consideration were taken. Furthermore, he must be sure that they were taken without bias. Unfortunately, many of the figures supplied by insurance companies are invalidated by this defect. Any physician who has ever done any examining for insurance companies knows that unless he is willing frequently to read low, the agent who patronizes him will soon seek elsewhere for someone who is more complaisant. This is not a pleasant statement to have to make, but the fact must be faced by all who would study blood pressure with statistical methods.

Actually if the blood pressure is taken by a conscientious observer and recorded accurately, the indirect method is accurate enough for clinical purposes. Hamilton, Woodbury, and Harper[33a] have compared blood-pressure readings obtained by the indirect and direct methods. They found that in most cases the indirect systolic values were a little too low, the indirect diastolic values too high, and consequently the pulse pressures too low. However, these authors agreed that the differences between the direct and indirect values are sufficiently small to justify the clinical use of the indirect method.

Studies by Robinow, Hamilton, Woodbury, and Volpitto[74a] who used the direct method for comparison, have shown that the width of the cuff as related to the size of the arm influences the accuracy of the result obtained by the indirect method. After extensive simultaneous studies of blood pressure by the direct and indirect methods with different widths of cuffs, they suggested three cuffs of different widths for the arms for children, that is, 2.5 cm for newborn infants, 5 cm. for small children, and 9 cm. for large children. They found that a cuff 13 cm. wide is satisfactory for measuring the blood pressure in the arm of an adult. If the person is unusually obese, a wider cuff must be used, and even then it will be difficult to obtain accurate readings by the indirect method.

Kotte, Iglauer, and McQuire[55b] found by comparison of blood pressures obtained by the direct and indirect methods that the femoral systolic pressure cannot be measured accurately with a standard (13 cm.) cuff and that a wider (15.5 cm.) cuff permits more accurate measurement of the systolic pressure. They found the femoral diastolic pressure obtained with either cuff grossly inaccurate in all subjects

In many ways, it would seem as if blood pressure ought to be taken under basal conditions. Addis[1] has shown that when the readings are made while the man or woman is still resting in bed before breakfast, the figures obtained are much lower and more constant than those obtained later in the day. The difficulty, of course, is that the method is not practical for everyday use, and it is questionable if the results obtained would warrant the extra inconvenience to the physician and the extra expense to the patient Perhaps what the physician needs most to know is not the

basal pressure, but the pressure that is present during the many hours of the day in which the patient is subject to the wear and tear of work, emotion, and fatigue.

It is probable also that much information of value could be secured by comparing the basal and the midday pressures. As Brown[11] and his students have shown, the only way in which to learn all the facts about blood pressure is to make readings at frequent intervals during the day and night, and daily over a period of at least a week. Anyone who has ever seen a record made in this way will realize how erroneous those conclusions are likely to be which are drawn from a few readings taken haphazardly in morning or afternoon, on Monday or on Saturday.

Let it be supposed that a physician has found on Monday morning in a certain patient a systolic pressure of 200 mm. of mercury. He gives a drug, for example, sodium nitrite, and asks the patient to return the next afternoon. He then finds a pressure of 170 mm. and congratulates himself on having obtained a good therapeutic result. But if the patient had failed to take the medicine, the reading might still have been 170 mm., because this is perhaps the normal afternoon pressure for this particular patient. As Brown has shown, it is almost impossible in any one case to judge of the value of some form of treatment until the cycle of normal changes in blood pressure in the particular man or woman is first studied.

As everyone knows, there are many more or less physiologic factors which are capable of influencing blood pressure and which should be taken into account in all determinations, especially in those that are to be used for statistical purposes or for comparison with those that have been taken by observers elsewhere. The most important of these factors will now be taken up *seriatim*.

PHYSIOLOGIC VARIATIONS OF NORMAL BLOOD PRESSURE

Posture: Sewall[82] and Ghrist[30] studied the blood pressures of normal persons as they were moved passively from the recumbent to the erect position, and found no significant change in the systolic readings; the diastolic pressure rose, on an average, about 12 mm. In Cruickshank's[20] group of subjects, the average pressure with the patients recumbent was 112 mm. systolic and 78 mm. diastolic, and with them sitting, 103 mm. systolic and 78 mm. diastolic.

Erlanger and Hooker[24] found that when their subjects stood up after lying down, some showed an increase, while others showed a decrease in systolic blood pressure. Lee,[59] who studied the pressures of 662 men, found 85 in whom the blood pressure, standing, was in excess of 140; when the 662 men lay down, there were only 31 with a pressure more than 140 mm. The change in posture was apparently an active one, *i. e.*, carried out by the person himself; unfortunately, Lee did not state in which position the blood pressure was taken first. His data lend some support to the view that systolic blood pressure is higher when the man or woman is standing.

Mortensen[69] studied the blood pressure of ninety normal girls, first recumbent and then after they had been tilted into the erect position. The

change produced a slight fall in the systolic and a greater rise in the diastolic pressure. Schneider and Truesdell[77] studied 2000 aviators whose average age was twenty-five years. In the recumbent position the mean systolic pressure was 118.0 ± 0.2 mm.; after they had stood up it was 120.3 ± 0.2 mm. At the same time the diastolic pressure rose, usually about 8 mm. Schneider and Truesdell quoted the results of four investigators, three of whom found an increase in the "recumbent" systolic pressure as compared with the "standing" or "sitting" pressure, and one who found lower pressures in the recumbent position. Sewall[illegible] concluded, after an analysis of several hundred observations, that the active change from the recumbent to the standing position will always bring about a rise in diastolic pressure. From this work it seems fairly obvious that when the subject of the experiment is moved passively, the change from the recumbent to the erect posture does not change the systolic pressure very much; when, however, the change of posture is an active one, brought about by the subject's own muscles, the pressure is raised; *i e*, with active change of position, the systolic and diastolic pressure rises.

Sleep: Lowering of blood pressure during sleep has been demonstrated by Landis,[56] Brooks and Carrol,[10] Brush and Fayerweather,[12] Campbell and Blankenhorn,[16] Mueller and Brown,[70] Tarchanoff,[illegible] Muller,[71] Howell,[41] and Katsch and Pansdorf.[51] MacWilliam[61] believed that restful and sound sleep lowered blood pressure, while unsound sleep caused by unpleasant dreams increased it. He believed that such rises in pressure might account for many of the vascular accidents which occur during the night. He found two cases in which during sleep the systolic pressure rose 40 and 70 mm. respectively. Hill[37,38] concluded that blood pressure falls during sleep only as much as it falls when a man lies awake in bed Brush and Fayerweather[12] found that it falls during the first hours of sleep, only to rise again gradually, so that on awakening it is higher than in the evening before Campbell and Blankenhorn[16] found the pressure at its lowest point in the fourth hour of sleep and believed that this low level was maintained for the rest of the night. Brooks and Carrol[10] found the lowest pressure after the first one or two hours of sleep. The pressure on awakening was lower than it was during the previous afternoon and it did not return to this high level until late the next afternoon. So far as they could see, it did not make any difference whether the man or woman slept during the day or at night. Landis[57] found pronounced rhythmic changes in blood pressure during sleep. Mueller and Brown[72] found the lowest pressure between the hours of 3 and 4 A. M, after which there was a gradual return to the usual morning level.

On summing up these studies, it appears that blood pressure normally falls during restful sleep. So far, observers do not agree as to the form of the normal curve of hourly fluctuation. It is probable that sleep of itself does not influence the blood pressure only in so much as it produces complete rest and relaxation.

Diurnal Variations: Mueller and Brown,[70] who took blood pressure readings every hour of the day and night in a group of twenty-six normal persons, found a gradual rise during the day and a fall during the night.

The high point in the curve came usually about 6 or 7 P. M. A study of Figs. 3 and 4 in their paper shows that there are three daily peaks; in Fig. 3, they come at 9 A. M., and at 1 and 7 P. M.; in Fig. 4, they come at noon, and at 3 and 7 P. M. These peaks can hardly be ascribed to the taking of food.

Weiss[94] found systolic readings at night 20 mm. higher than those made at 9 A. M., and Zadek[97] found a midafternoon rise independent of the midday meal. Hill,[37,38] studying his own blood pressure, found it higher after a day's work than in the morning. Brown[11] trained a young man with severe hypertension to measure his own blood pressure several times a day for months and years. The curves so obtained showed a definite daily cycle with the pressure lower in the morning than in the afternoon. In addition, there was a striking weekly cycle with a gradual rise from Thursday to Sunday and then a fall again until Wednesday. The rise from Thursday to Saturday might easily be ascribed to increasing fatigue, but the high point on Sunday was hard to understand until the man, a bachelor and a steamfitter, explained that on Saturday and Sunday his routine was disturbed; he missed the tranquilizing effect of work and, in consequence, became restless and irritable.

Faught[26] found a gradual rise in blood pressure during the day. Hensen[36] who studied a healthy girl who remained in bed for nineteen days, found that the evening systolic pressure exceeded the early morning pressure by from 5 to 15 mm. Sigler[87] found hourly variations in blood pressure, independent of psychic effects, meals, posture, etc. Weysse and Lutz[95] found similar variations which they thought were due largely to the taking of food. Jellinek[45] studied two healthy soldiers on sentry duty and found the systolic pressure somewhat lower in the evening than in the morning.

Emotions: Emotions tend to raise blood pressure, as has been shown by Cannon,[17] Schrumpf,[79] Marston,[63,64] Cabot,[14] Tixier,[91] Addis,[1] O'Hare,[73] Kilborn,[54] Diehl and Lees,[21] Scott,[80] Dumas, Lamache and Dubar,[23] Tigerstedt,[90] and Grollman.[32] A rise can be caused by feelings of pleasure, anger, fright, apprehension, excitement, and general nervousness. Marston[63] found a fall in blood pressure resulting from feelings of compliance and submission. Scott[80] found no correlation between the strength of the emotion, as judged by the subject, and the amount of change in pressure. Landis and Gillette,[57,58] who studied the blood pressure of persons being questioned, concluded that the slight, usually 3 mm., rise observed sometimes during attempts at deception were too small to have diagnostic value.

The effect of emotion on blood pressure can be seen in the well-known fact that the reading is likely to be higher at the first interview than at subsequent ones. Thus, Diehl and Lees[21] studied 100 University freshmen who had been judged to be normal on the basis of a physical examination made shortly after matriculation. Taking the first readings made on each man, the mean systolic blood pressure was found to be 118.7 $\pm$ 0.7. Subsequent readings were then made every five minutes for an hour. After the first five minutes there was a mean fall in pressure of 2.9 $\pm$ 0.9 mm.; after the second five minutes there was another mean fall of 3.7 $\pm$ 1.0 mm.; after another five minutes the readings became fairly stable with a mean of 111.0 mm.

Gallavardin and Haour,[29] in a study of 100 persons, found a systolic blood pressure from 25 to 35 mm. higher at the first reading than it was later when the subjects were accustomed to the procedure. O'Hare[73] found systolic blood pressures 21 mm. and diastolic pressures 10 mm. higher on the first measurement than on later ones when the subjects of the observations had been allowed to rest for from five to seventy minutes. Sigler[85] attempted to eliminate psychic influences by isolating the examining room as far as possible from outside influences, and by allowing the patient to rest from three to five minutes. He made blood pressure determinations every minute for from ten to twenty-five minutes His study of seventy-two normal persons showed practically no variation of pressure in fifty, but variations of from 10 to 30 mm. in the other twenty-two He did not state whether these variations represented increases or decreases in the level of blood pressure. Alvarez,[3] who compared blood pressure readings made on 100 office patients on the occasions of the first and second visits, found differences sometimes as high as 40 mm. When he compared the sums of the two measurements he found them practically identical

There is no doubt that in some persons blood pressure is much more variable than in others, and this difference may some day be found to have great significance. Allen, Bowing and Rowntree[2] showed that there is almost always a marked fall in blood pressure when a patient is put to bed and kept there for a few days. *For this reason it is impossible to judge of the effect of any therapeutic measure until the pressure has become stable at the new, resting, level. It is unfortunate that most of the physicians who in the past have attempted to evaluate methods of treating patients with hypertension have been unaware of this fact. It should be obvious from all this that a single measurement of blood pressure, especially in a person who is anxious or emotionally unstable, can have little value.*

Muscular Effort: Cannon[17] showed that great muscular effort increases the blood pressure. He believed this to be due to the forcing of blood from the abdominal vessels into other parts of the body During effort, the diaphragm and muscles of the abdominal wall are probably contracted so as to stiffen the trunk and thus offer support for the arms. Cook and Briggs[18] found an increase in the blood pressure of infants during nursing. Erlanger and Hooker[24] noticed that moderate exercise will sometimes diminish diastolic pressure and severe exercise will increase it. McCurdy[67] concluded that muscular effort can increase systolic pressure by as much as 70 mm., and Schneider and Truesdell[77] found that it can increase also the diastolic pressure. Addis[1] found during study of ten normal persons that after short periods of exercise the mean systolic blood pressure rose from 121 to 137 mm., and after longer periods it rose to 168 mm. Systolic pressure appears, then, to be increased by muscular effort of any degree; diastolic blood pressure, on the other hand, is decreased by moderate exercise and increased by severe muscular effort.

Meals: Increased blood pressure during or shortly after eating has been noted by Faught,[26] Loeper,[60] Cook and Briggs,[18] Gumprecht,[33] Sommerfeld,[84] Hayashi,[35] Weiss,[94] Jellinek,[45] Zadek,[97] and May.[66] Weiss,[94] however, found decreases after breakfast and luncheon and a rise after the evening meal. Erlanger and Hooker[24] found a similar variable response

to meals but thought there was a fairly constant tendency to an increase in pulse pressure. May[66] believed that a postprandial increase in blood pressure is to be found only in health; during illness there is likely to be a systolic pressure and an equal fall in the diastolic pressure following dinner and supper. Maximowitsch and Rieder,[65] and Karrenstein[50] found an increase in blood pressure after the drinking of fluids.

Difference in Blood Pressure in the Two Arms: Kay and Gardner[52] had their attention directed to differences in pressure in the two arms by the discovery of a person with a reading of 130 mm. systolic pressure in the left arm and 165 mm. in the right. They studied a group of 125 persons and found twenty-five with significant differences between the measurements in the two arms. The difference was at times as great as 40 mm. in the systolic pressure and 20 mm. in the diastolic pressure. Stephens[85] found that pressures tend to be on the average from 3 to 4 mm. higher in the right arm than in the left arm. Bodenstab[9] examined 100 patients and found ten with different systolic and four with different diastolic pressure readings in the two arms. In these persons neither arm showed a consistently higher pressure. Unfortunately, in all but two cases he failed to state whether the first reading was the higher, a fact of great importance.[21]

If especial accuracy is desired in determining the differences in blood pressures in two extremities, the blood pressure should be determined simultaneously. This is more important for persons who have hypertension than for others, inasmuch as marked vascular hyperreactivity may cause a change in blood pressure of considerable degree between successive measurements.

Korns and Guinand[55a] determined blood pressures by the indirect method simultaneously in both arms of 731 men and 269 women. They found inequality of blood pressure in 37.8 per cent. In three-fourths of the subjects the higher reading was on the right arm. They concluded that, "sphygmic inequality without organic disease is probably always transitory, and it is reasonably certain that all normal persons manifest it at one time or another." They found that the inequality involved only the systolic pressures or only the diastolic pressures in some cases. If both were different, the inequality might be concordant (both systolic and diastolic blood pressure higher in the same arm) or discordant (the systolic higher in one arm and the diastolic in the other).

Differences in Blood Pressure in the Arm and Leg: Hamilton and his associates measured the blood pressure by the direct method after arterial punctures in the arm and leg of thirty human subjects. Their findings demonstrated conclusively that the blood pressure is higher in the leg than in the arm. Cady[15a] consistently found a higher systolic pressure in the leg than in the arm when measured by the indirect method.

Gambill and Hines[29a] found the difference of blood pressure in the arm and thigh of 112 human subjects to vary greatly. The values varied not only from subject to subject but also in the same subject, depending on various circumstances, such as the emotional state and the position of the subject. The average differences when the patient was in the horizontal position were 35 mm. systolic and 27 mm. diastolic. When the upright

position was assumed, the differences were strikingly greater, measuring 78 mm. systolic and 66 mm. diastolic. These differences in blood pressure were correlated roughly with the range of blood pressure of each individual; the normal nonhyperacting subject had a smaller difference in blood pressure between the arm and leg in either position than the normal hyperreacting or hypertensive hyperreacting subject.

Position of the Arm: Kahn[48] found on studying twenty-seven normal persons that there was an average fall of 55 mm in the systolic pressure when he raised the arm from the dependent to the vertical position.

Berry[8a] studied the effect of change in body position on the blood pressure as related to the position of the arm on which the blood pressure was being determined. He concluded that the diastolic pressure increased when the arm was lowered from a horizontal to a pendent position due to the effect of gravity and of venous engorgement of the arm He advised that the blood pressure of an erect subject be determined as follows. The subject's arm is elevated above his head. The sphygmomanometer cuff is inflated rapidly to produce a pressure of more than the systolic pressure; the arm is lowered to the level of the heart and the usual auscultatory method of determining blood pressure is initiated.

When this method was employed, Berry found that the diastolic pressure of normal subjects did not increase as subjects changed from the supine to the erect position.

Menstruation and Pregnancy: Studies of Griffith and his associates[31] on five subjects showed that the systolic pressure (standing) is lowest during the latter part of the intermenstrual period. It tended to be highest during the week of menstruation. The work of Moore and Cooper[68] showed that menstruation does not seem to affect the normal weekly rhythmic cycle of change in systolic pressure.

Stieglitz[86] found a gradual rise in arterial tension during the final month of pregnancy. There was a fall immediately after parturition and a rise again with the onset of lactation. Cornell,[19] who studied 1000 women, concluded that in the largest most normal group, the pressure was lower throughout pregnancy than in normal nonpregnant women Much of the literature on the subject is summarized in his paper Seward and Seward[96] found that pregnancy was accompanied by an early rise and later fall in the systolic blood pressure.

Constipation: The study made by Alvarez, McCalla, and Zimmermann[5] on office patients showed that constipation has little if any effect on blood pressure. No significant difference was found between the mean pressures of constipated and nonconstipated men. In women, constipation seemed to lower pressure slightly.

Alcohol: The studies of Alvarez and Stanley[6] on inmates of a large state prison indicate that the more or less constant use of alcohol does not permanently affect blood pressure. If anything, it causes it to be lower in the later years of life.

Tobacco: The use of tobacco does not seem to have much permanent effect on blood pressure. Alvarez and Stanley[6] found that nonsmokers have slightly lower pressures than smokers. According to Johnson,[46] the

act of smoking, if it has any effect at all, slightly lowers the pressure. Janeway[44] found a slight increase during smoking.

Herrell and Cusick[36a] observed ten patients who had a marked rise in the systolic and diastolic pressures following the smoking of one or two cigarettes. Cusick measured the retinal arterioles of some of these patients and demonstrated measurable vasospastic changes in the retinal arterioles during inhalation of tobacco smoke.

Hines and Roth[40a] studied the effect on the blood pressure of a standard smoking test and compared the response of blood pressure to smoking tobacco to the response of blood pressure to the cold pressor test. Thirty subjects who had normal blood pressures and fifty-six who had essential hypertension were tested. They found that cigarette smoke produced an elevation of blood pressure in the majority of individuals tested. The excessive rises in blood pressure from smoking occurred largely in the subjects whose blood pressures responded excessively to the cold pressor test. They concluded, however, that the effect of smoking tobacco on the blood pressure was not due entirely to the nonspecific stimulus of smoking on a hyperreactive vascular system but that some element in the tobacco smoke caused elevation of the blood pressure by producing vasoconstriction.

Weight: As Alvarez and Zimmermann[7] have pointed out, it is not safe to compare mean blood pressure in any two groups of persons unless the weights of the persons are known and factors deduced from these weights are used to correct the figures expressing mean pressure. The technic for making the correction is similar to one used by satisticians in the correction of mortality rates. Unfortunately, more information is needed in regard to this relationship between weights and pressure, and until it is available, the correction of means will be somewhat unsatisfactory. The tables that are to be found in articles by Symonds,[88] Alvarez and Zimmermann,[7] Huber,[42] Hartman and Ghrist,[34] Burlage[13] and Alvarez and Stanley[11] are all somewhat different.

It has never been demonstrated clearly that the higher blood pressure readings obtained in obese persons are not due mainly to the greater difficulty in compressing the brachial artery in a fat, flabby arm. Against such an explanation is the fact demonstrated by Symonds,[88] Alvarez and Zimmermann[7] and Alvarez and Stanley[6] that fatness before the age of thirty-five or forty years does not have much effect on blood pressure. It is after this that most of the effect comes.

Body Build: It has been generally assumed that blood pressure tends to be higher in short, stocky, short-necked persons than in tall, thin, rangy ones, but the anthropologic and statistical study of Alvarez and Stanley[6] did not reveal any significant correlation between blood pressure and the pyknic index. This index expresses numerically the relation between the bulk of the thorax and the length of the legs.

Height and Surface Area: Alvarez and Stanley[6] could not find in state prisoners any significant correlation between systolic blood pressure and either height or surface area.

Climate, Temperature and Race: Tung[92] compared the pressures of fifty-eight Americans before and after they had resided for two or three

years in China. The average figures in America were 118 mm. systolic and 76 mm. diastolic; in China they were 109 and 65 mm. Foster[27] examined thirty-four men and women after a residence of one or more years in China. The average systolic blood pressure was from 8 to 14 mm. lower in China than in America. Forty members of the faculty of the Peking Medical College showed a mean pressure 9 mm. lower than it was when they were living in America. These conclusions are based on single blood pressure determinations taken in America and in China, and are of doubtful significance. Furthermore, Tung found an increase in blood pressure in China in fifteen per cent and no change in twenty-one per cent of the fifty-eight subjects tested.

Kilborn[53] examined 700 university students in Szechwan (latitude 30°) and found a mean systolic pressure of 111 mm. and a diastolic of 70 mm. Nine Canadian and American boys raised in Szechwan, with a mean age of fifteen years, showed a mean systolic pressure of 120 mm and a diastolic of 80 mm. The latter group is small for comparison with the Szechwanese students, but so far as the data go, they indicate that the difference observed is due to differences in race or amount or quality of food and not to climate. Kao[49] found that students in Hunan (latitude 34°) had systolic pressures higher than those of students in Canton (latitude 23°). Cadbury[15] studied 774 Chinese students in Canton. Those between the ages of seven and fourteen years were found to have a mean systolic pressure of 83 mm. and a diastolic of 51 mm.; those between the ages of fifteen and twenty years showed pressures of 101 and 62 mm., and those between the ages of twenty-one and thirty years showed pressures of 101 and 68 mm. The number of subjects studied is too small to permit any conclusions in regard to the possible effects of climate or temperature on the blood pressure of persons living in different environments or on persons of different races.

Brown,[11] in an extensive study of daily and monthly variations in blood pressure, found a tendency to low readings in warm weather. Alvarez and Stanley[6] examined seventy-four prisoners on a warm day and 135 on a cool day. The mean systolic pressure of the first group was 118.8 ± 1.10 mm. and of the second 122.7 ± 0.8 mm. Since different groups were used, this evidence is only suggestive.

On the whole, there would seem to be little doubt that blood pressure readings that are to be used for statistical purposes should always be accompanied by a record of the temperature of the environment at the time of the study. It seems probable that the person who is perspiring freely and whose tissues are relaxed by warmth will have a lower pressure than the one who is somewhat tense from cold. It may be found some day that the big differences observed in the mean pressures of several thousand university freshmen at the same school but in different years are due in part to differences in temperature during the week in which the examinations are made.[9]

Barometric Pressure: According to Franke,[28] there is some correlation between barometric pressure and blood pressure, but his published figures are not convincing.

Comment: In order that a blood pressure reading may be of statistical value, it should be made carefully with a good mercury manometer and a cuff of correct width. The mercury should be allowed to fall gradually and the reading should not be made carelessly to the nearest multiple of ten. If a second reading is made, the cuff should first be deflated and the arm allowed a moment's rest. Readings should be made with the auscultatory method. All the subjects should be examined in the same position and the same arm (right or left) should be used. Note should be made on the length of time that the subject waited before examination; also whether he hurried to the appointment, or, while waiting, stood partly dressed in a cold room, took a warm bath, or did anything out of the ordinary.

The temperature of the environment should be noted and also the time of day, and day of week. If more than one reading is made at short intervals, all of the subjects must be treated in the same way, and only one method must be followed in reporting the results. It is not good statistical practice to use the first record made on ten men and then to juggle with the eleventh man until his measurement is brought down or up to the desired or expected point. It will be necessary, of course, to include data in regard to sex, age, and weight. In any published report of blood pressures, it should be stated whether weight was taken with or without clothes.

The presence of a fast pulse should be noted, as this can probably account for an increase in systolic blood pressure. Note should be made also of the presence of a cold or other transient infection, or of fatigue from a "hard night out." Finally, in every paper on blood pressure, all the data should be presented in the form of a distribution table, so that they can be used again and analyzed further by subsequent students of the subject.

STANDARDIZATION OF BLOOD-PRESSURE DETERMINATIONS

The American Heart Association[16a] in conjoint action with the British Heart Association has made the following recommendation for the standardization of determinations of blood pressure:

Blood-Pressure Equipment: The blood-pressure equipment to be used, whether mercurial or aneroid, should be in good condition and calibrated at yearly intervals—more often if defects are suspected. (Mercurial preferred—British Committee.)

The Patient: The patient should be comfortably seated (or lying—British Committee), with the arms slightly flexed and the whole forearm supported at heart level on a smooth surface. If readings are taken in any other position, a notation of that fact should be made. The patient should be allowed time to recover from any recent exercise or excitement. There should be no constriction of the arm by clothes, etc.

Position and Method of Application of the Cuff: A standard-sized cuff containing a rubber bag 12 to 13 cm. in width should be used. A completely deflated cuff should be applied snugly and evenly around the arm with the lower edge about 2.5 cm. (1 inch) above the antecubital space and with the rubber bag applied over the inner aspect of the arm. The

cuff should be of such a type and applied in such a manner that inflation causes neither bulging nor displacement.

Significance of Palpatory and Auscultatory Levels: In all cases palpation should be used as a check on auscultatory readings. The pressure in the cuff should be quickly increased in steps of 10 mm. Hg until the radial pulse disappears, and then allowed to fall rapidly. If the radial pulse returns at a higher level than that at which the first sound is heard, the palpatory reading should be accepted as the systolic pressure, otherwise, the auscultatory reading should be accepted.

Position and Method of Application of Stethoscope: The stethoscope should be placed over the previously palpated brachial artery in the antecubital space, not in contact with the cuff. No opening should exist between the lip of the stethoscope and the skin, this should be accomplished with the minimum pressure possible. The hand may be pronated or supinated, depending on which position yields the clearest brachial pulse sounds.

Determination of the Systolic Pressure: The cuff should be rapidly inflated to a pressure about 30 mm. above the level at which the radial pulse can be palpated. The cuff should then be deflated at the rate of 2 to 3 mm. Hg per second. The level at which the first sound regularly appears should be considered the systolic pressure, unless, as pointed out above, the palpatory level is higher, in which event the palpatory level should be accepted. This should be noted.

Determination of the Diastolic Pressure and the Pulse Pressure: With the continued deflation of the cuff, the point at which the sounds suddenly become dull and muffled should be known as the diastolic pressure. If there is a difference between that point and the level at which the sounds completely disappear, the American Committee recommends that the latter reading should be regarded also as the diastolic pressure. This should then be recorded in the following form: RT* (or LT†) 140/80-70, or 140/70-0. If these two levels are identical the blood pressure should be recorded as follows: 140/70-70. The cuff should be completely deflated before any further determinations are made.

The British Committee believes that except in aortic regurgitation it is nearly always possible to decide the point at which the change comes, and that this is the only reading which should be recorded.

PRESSOR TESTS

Cold Pressure Test: A simple test for this response, first described by Hines and Brown,[39] consists of immersing the patient's hand in ice water and determining the vasomotor effect as shown by changes in the blood pressure. It was found that ninety-nine per cent of patients responded by a rise in pressure, and that this response was reasonably constant over a period of time. In a later report, these authors[40] report data accumulated from the study of 571 patients so tested. The following technic was observed:

* RT = right arm.
† LT = left arm.

The patient is allowed to rest, in a supine position, for twenty to sixty minutes in a quiet room. The basal level of pressure is approximated from several readings, the cuff of the sphygmomanometer is adjusted on one arm of the patient, and the opposite hand and wrist is immersed in ice water. The reading at the end of thirty and sixty seconds is ascertained, the hand removed from the ice water, and readings are taken every two minutes until the level is again reached. The maximum response, or "ceiling," which is frequently obtained in thirty seconds and held for a variable period of time, and the amount of increase, or "range," are the two important values obtained in this way.

These reactions seem to be constant over long periods of time, and are characteristic for the three groups—normal, normal hyperreactives, and hypertensives—into which the authors have divided their subjects.

Normal (Normal Blood Pressure): The mean increase was 11.4 mm. systolic and 10.6 mm. diastolic, with a range of 0 to 22 mm.

Normal Hyperreactive (Blood Pressure within Normal Limits): Mean increase was 29.4 mm. systolic, and 24.5 mm. diastolic. This group, in the opinion of Hines and Brown, is most important from a prognostic standpoint. It is not a definitely established fact that this reaction is a precursor of hypertension, but there is a very strong probability that it will be so proved. Seventy-eight of the ninety patients in this group gave a positive hypertensive family history, while only fourteen per cent of the first group had positive histories. Three of the patients examined in 1932 had developed essential hypertension by 1936.

Essential Hypertension: The mean rise was 47.2 mm. systolic and 34.3 mm. diastolic in the organic group, and 34.4 mm. and 25.4 mm. in the preorganic. All these patients had high "ceiling" values.

The Breath-Holding Test: Ayman and Goldshine[7a] have devised a pressor test in which the holding of the breath for a certain period is employed as a standard stimulus. The technic which they advised is as follows:

With the subject sitting in a quiet room, the blood pressure is determined at intervals of about five minutes until a basal level is obtained. The subject is then asked to compress his nostrils suddenly with the fingers of the free hand and simultaneously close the mouth by compressing the lips. He is cautioned in advance and also at the time of the test not to inhale or exhale excessively just prior to the test. Both these points are checked by observation. Actually, the command to close the nose and mouth is given at the moment at which normal quiet expiration has occurred. The subject is told to keep the nose and mouth closed without allowing the slightest amount of air to pass in or out. Furthermore he is advised that the time of holding the breath is to be twenty seconds, and that the final few seconds are usually attended by discomfort. He is also asked to relax his chest and body. During the last five seconds of holding the breath, the subject is strongly urged to resist the impulse to breathe.

As soon as holding the breath is begun, the observer pumps up the manometer to the level of the systolic pressure and follows the systolic pressure during the twenty seconds of the test. If it rises, the elevation is greatest during the last half of the period. At exactly the end of the twenty

seconds, as determined by the second hand of an ordinary watch, the final systolic reading is noted. The subject is then told to breathe again and the blood-pressure cuff is deflated. The blood pressure returns to or falls slightly below the original basal level within a minute or two After a few minutes of rest and a return to the basal level, the test is repeated, but this time at the start of the test the cuff is inflated to the level of the diastolic pressure, and the rise of diastolic pressure is followed during the test Although it is possible to determine both systolic and diastolic blood pressure in one period the time necessary to read both systolic and diastolic pressures will carry the period of holding the breath beyond twenty seconds and make for greater discomfort for the subject and inaccuracy in the diastolic reading. The separate determinations of the rise in the systolic and diastolic blood pressures constitute together one complete breath-holding test.

The breath-holding test is simple and relatively easy to perform It is not as reliable as the cold pressor test, inasmuch as the detailed cooperation of the subject is required and in some instances holding the breath is difficult to control.

Comment: The various pressor tests have been of aid in demonstrating that the blood pressure of some individuals who have presumably normal blood pressure and almost all who have early essential hypertension reacts excessively. Such observations have emphasized the inherent variability of the blood pressure and the importance of the role of this inherent variability in any consideration of what is normal blood pressure.

The theory that normal hyperreactors form the group from which hypertensives eventually will come is an attractive one and there is some evidence in support of this contention. However, at present the results of the pressor tests should not be used routinely as a prognostic sign in the interpretation of the response of the blood pressure of any particular individual.

NORMAL BLOOD PRESSURE

The term "normal blood pressure" must, of course, always refer to the ideal or commonest pressure found in persons of average weight and of a certain age. Obviously, it is difficult to get measurements on large groups of unselected or presumably normal persons. The ideal way would be perhaps to put up booths in various parts of several towns and cities and there to make a pressure reading on each of the first 5000 persons to pass by. Since this can hardly be done, the next best plan is to examine students, soldiers, employees of large institutions, state prisoners, and inmates of old people's homes. Office patients are not suitable because they constitute a selected group. Similarly, soldiers and aviators are not entirely satisfactory because they have already been selected for their special fitness and freedom from defects Applicants for insurance are not always satisfactory because so many apply the minute they have reason to believe they are ill. Furthermore, as has already been pointed out, in their case the examiner so commonly works under duress.

Discordance in Results Reported by Different Observers: In a review of the reports of the various investigators, one of the great difficulties encountered arises from the fact that one physician will measure pressures

in children, another in high school students, another in college students, another in soldiers or prisoners or insurance "risks" of middleage, and another in aged inmates of almshouses or old people's homes. Each one plots a part of the desired curves expressing the relation in males and females between blood pressure and age, but unfortunately, when these parts are brought together onto one sheet of coordinate paper, their ends rarely meet, and many puzzles remain for solution.

As Alvarez[3,4] has shown, even when one set of examiners works fairly carefully in a university infirmary from year to year, decided variations will be found in the mean pressure of the thousands of freshmen examined. These variations are far too large to be accidental, and they have been observed in more than one institution. They have been noticed also by insurance examiners.[68] It would seem that some of the differences must be due to personal factors; others may well be due to certain cycles of human metabolism which are just beginning to be recognized;[11,31,68] others again may be due to the fact that some examinations were made predominantly in the morning and others predominantly in the afternoon. In this connection, what is probably a most illuminating observation was made by Diehl and Lees[21] as they studied 100 male university students. The mean systolic pressure in the morning was 115.0 ± 0.3 mm. and in the afternoon 124.1 ± 0.3 mm. Such a difference alone would be enough to explain all the variations which have been found in standards of normal offered by different investigators such as in almost identical groups as studied by Jackson[43] and Diehl and Sutherland,[22] granting that some did most of their examining in the morning and others in the afternoon.

Desirability of Using the Mode and Not the Mean: It is unfortunate that almost every attempt made so far to set up standards of normal blood pressure has been more or less invalidated by the fact that the average or the index of central tendency used has been the arithmetic mean and not the mode. The man who is not statistically trained will always use the one average with which he is acquainted and this, unfortunately, is the arithmetic mean As everyone knows, this is obtained by adding the measurements and dividing by their number. This one out of several possible averages suffers from the serious defect that it is influenced, sometimes markedly, by data secured from abnormal persons. Actually, if there are enough abnormal persons in a group, the arithmetic mean will have practically no value, because it will represent a compromise between the normal and the abnormal figures.

To give an example: An anthropologist may be studying the stature of a group of persons living on a small island in the Pacific. The laborers on this island probably are Japanese and the overseers and the men in the business office are Americans. If the anthropologist were to put down at the bottom of a sheet of paper a row of figures representing stature in inches and above each figure a dot for each man of that particular height, he would find when he had finished that the dots had made two mounds, one with a peak or mode perhaps at about five feet four inches, and another with a peak at about five feet nine inches. Another anthropologist seeing this chart would know immediately that his colleague had been dealing

with a composite, heterogeneous population: One made up of a large group of persons of low stature together with a small group with high stature. The mean or average stature of such a composite group would be expressed by a figure devoid of value or interest, because it would fail to tell anything about the stature of either Japanese or Americans. The arithmetic mean fails also to warn the investigator that he is dealing with a composite group.

It is greatly to be hoped, therefore, that in all future work on blood pressure little attention will be paid to arithmetic means but that, instead, modes for the different ages will be published. It is really this mode that the physician wants to locate when he is searching for criteria of normal. He does not want a compromise figure; he wants to know the commonest or most usual pressure in supposedly normal persons, and this obviously is to be found on the scale below the principal peak in the distribution polygon. Another valuable bit of information that the distribution polygon supplies is the range of normal values.

Influence of Age: Systolic pressure in newborn infants of both sexes has been found to be between 43 and 55 mm.[74,75] It tends to rise rapidly so that at the end of the first week it is about 60 mm. and by the end of the first month, 82 mm.[81] Judson and Nicholson,[47] who studied 1244 normal children, found a systolic blood pressure of approximately 91 mm. in the group aged from three to nine years. The pressure was about 99 mm. in children aged from ten to twelve years, and it was approximately 104 mm. in the years from thirteen to fourteen.

The diastolic pressure did not show much change with the increasing age. Faber and James[25] studied 1101 boys and girls with ages ranging from three to seventeen years. In both sexes systolic pressure increased from about 89 mm. at the age of four years to 115 mm. at the age of sixteen years. The diastolic pressure ranged from 60 to 75 mm.

Stocks and Karn[97] made a careful analysis of blood pressure in 1163 normal persons aged from five to twenty-four years inclusive. Unfortunately, mose of the age groups were too small for adequate statistical treatment. Their figures for mean systolic pressure showed a steady increase from 85 mm. at the age of five years to 130 mm at the age of seventeen years. After this there was no increase.

Burlage,[13] who studied 1700 girls from school and college, found a rapid increase in systolic blood pressure from 104 mm. at nine years to approximately 124 mm. at fourteen years. *The pressure remained about 124 mm. during the fifteenth year and then there was a rapid fall of about 10 mm. to the age of eighteen. After this, until the age of twenty-six years, the pressure remained fairly constant at a level of about 110 mm. The diastolic pressure rose evenly from 63 mm. at the age of nine years to about 76 mm. at the age of fourteen years and after this remained constant.*

Alvarez[4] studied 365 boys and 288 girls in high school. There were three groups corresponding to ages of thirteen, fourteen, and fifteen years. During this short period of life the mean systolic pressure of the boys rose from 110 to 121 mm. while that of the girls fell from 121 to 120. The range of the measurements was much wider in boys than in girls and there was much more hypertension found among them than among the girls; in

fact, this defect was found commonly among the boys, some of whom were normal enough to be taking a successful part in athletics. The crude mode of the boys' pressure ranged during the three years from about 112 to 122 mm, while that of the girls remained constant at about 122 mm. The measurements were made with the auscultatory method and with the subjects sitting.

Kilborn[54] has emphasized the variability of blood pressure in young persons. He studied fifty-one students at four different times: (1) About the close of the academic year when examinations were due; (2) in September at the close of summer vacation; (3) just before the Christmas examinations, and (4) in the spring about the time when there happened to be some violent agitation among the students. He found the blood pressures greatest at the fourth determination and lowest at the second. Tigerstedt[90] found similar rises in blood pressure before examinations.

In a study of the reactions of blood pressure to a standard stimulus (cold pressor test) of 400 school children, Hines[38a] found that eighteen per cent of them were hyperreactive in respect to changes in both the systolic and diastolic pressures. The reaction of the diastolic pressure was much greater in children than in adults. In the group with "normal" (minimal) responses the mean increase was 12.6 mm. for the systolic and 14.0 mm. for the diastolic pressures. In the hyperreactive group the mean rise in systolic pressure was 33.8 mm. and in diastolic pressure 33 8 mm. The reaction of the blood pressure was greatest during prepuberty and puberty. Six pairs of identical twins were tested. The basal readings and responses to the test were almost identical in each pair.

Graham, Hines, and Gage[30a] studied the blood pressure of 3580 children from five to sixteen years of age, inclusive. Twenty-five thousand determinations were made by one physician (Graham) who followed the children's progress for fifteen years. The blood-pressure readings were all recorded under the same circumstances and by use of the same technic. The modal systolic pressure ranged from 92 mm. at the age of five years to 122 mm. at the age of sixteen years. The corresponding diastolic pressures ranged from 52 to 62 mm. The variation in the blood-pressure readings increased with age and was more pronounced in girls from ten to thirteen years of age than in boys of the same age.

Probably the most extensive studies made on college students have been reported by Alvarez.[3,4] In his second paper he analyzed the pressures of 6000 men and 8934 women. Among the men, the mean systolic pressure rose from 129.5 mm. at the age of sixteen, to 130 mm. at the ages of seventeen and eighteen years. After this the pressure dropped gradually to 127 mm. at the age of thirty years. The mean for the women was about 118 mm. at the ages of sixteen and seventeen years. After this it dropped steadily to the age of twenty-four, and after the age twenty-six it rose steadily to 119 mm. at the age of forty. The modal or most typical systolic pressure for the men fell from 127 mm. at the age of sixteen to 118 mm. at the age of twenty-eight; after this it rose. The modal pressure for the women dropped rapidly from 118 mm. at the age of sixteen to 111 mm. at the age of twenty-four; after this it rose to 116 mm. at the age of forty.

This tendency for the blood pressure to show a slight drop between the ages of seventeen and twenty-five may seem surprising to many physicians, but its existence has been definitely confirmed by several investigators, and actually, when the data published by insurance examiners[94] are studied more carefully, it will be found that they show a somewhat similar absence of a rise until after the age of forty years. In a series of 42,133 accepted "risks" of normal weight, the mean systolic pressure remained between 123 and 124 mm. until the age of thirty-nine years.

Alvarez[3,4] was surprised to find so many boys and college students with high pressure and at first rather doubted the accuracy of his measurements, but his observations have since been confirmed by several investigators working in different colleges. It now seems probable that there is an unusual degree of lability of blood pressure among boys and youths about the ages of seventeen and eighteen years. *This may perhaps be due to a greater sensitiveness of sympathetic nerves or to a greater responsiveness to emotion, and to such excitement as is occasioned by a physical examination.* Twenty-two per cent of the male freshmen and two per cent of the female freshmen at the University of California were found to have a systolic pressure exceeding 140 mm. As was shown by Diehl and Sutherland,[22] many of the high pressures are not constant and do not represent true hypertension. They doubtless have some significance in regard to the later health of the individual, but only time will tell what it is.

Diehl and Sutherland,[22] who worked with students at the University of Minnesota, found, as Alvarez did, that many show a high pressure at the first examination. In 1922, with 1686 male freshmen, the mean systolic pressure was 126.9 ± 0.2 mm. In the years 1923 and 1924 blood pressure was taken during the examination of 4346 more students. This time all those with a pressure higher than 140 mm. were held for several more readings. These later readings were usually lower than the first, and when they were averaged with the data secured from students who had normal pressures to begin with, a mean of 122.7 ± 0.1 mm. was obtained.

Barach and Mark[8] studied 656 young men between the ages of nineteen and twenty-five years. They found ninety per cent with systolic pressures less than 150 mm. and eighty-seven per cent with diastolic pressures less than 100 mm.

Lee[59] studied 662 freshmen and found a mean systolic pressure of 120 mm. and a diastolic of 80 mm. Woley[90] studied 1000 healthy persons between the ages of fifteen and sixty-five years. The palpatory method was used. The mean systolic blood pressure of the men was 127.5 mm. and of the women 120 mm.

Addis[1] studied soldiers for basal and active pressures. To get the basal pressure, the soldier was awakened in the morning by the application of the cuff to the arm. The mean pressure obtained in this way in the case of sixty-six normal men was systolic, 99 mm., and diastolic, 71 mm. After the men had been up and about, the corresponding figures were 127 and 78 mm.

Alvarez and Stanley[6] studied blood pressures in 6000 state prisoners. They found that modal blood pressures remained almost constant, about

115 mm. from youth to old age. This is perhaps a little lower than the corresponding figure for men out in the world, but it must be remembered that prisoners are not fatigued or worried by the struggle involved in making a living; to a certain extent, then, their pressures are basal. The mean pressure was fairly constant, about 117 mm., until the age of forty years; after this it rose. The evidence indicates that most of the men who had hypertension at the age of forty years had it at the age of twenty years, and that a pressure of 115 mm. is just as normal, and a pressure of 145 is just as abnormal, in an old man as in a young man. The modal diastolic blood pressure was 68.5 mm. in the younger men and 73 mm. in the older men.

Saller[76] studied the blood pressures of 7382 men and 5197 women between the ages of twenty-one and eighty-nine years. He found that the range of systolic blood pressure for normal men remained between 98 and 144 mm. during the ages between twenty-one and forty-seven years, inclusive. The range for normal women between the ages of twenty-one and thirty-five years was from 99 to 138 mm.; between the ages of thirty-five and forty-seven years it was from 100 to 155 mm. His study indicated an increase in the normal systolic pressure following the menopause of women and following the age of fifty years of men

Russek, Rath, Zohman, and Miller[75a] analyzed the readings of blood pressure of 5331 white men between the ages of forty and ninety-five years. They found the average "normal" systolic pressure increased progressively from 129.6 mm. for the group aged forty to forty-nine years, to 134.1 mm. for those aged eighty to ninety-five years. The frequency of upper levels of "normal" systolic pressure (140 to 149 mm.) was appreciably greater in the older subjects. The average "normal" diastolic pressure tended to decrease progressively from 80.9 mm. for those aged forty to forty-nine years to 74.5 mm. for the group eighty to eighty-five years of age. The diastolic pressures were less than 70 mm. in one of the older age groups. These authors concluded that the old maxim "100 plus the age" actually may be a fair index of the normal systolic pressure.

Miller[67a] studied the effect of increasing age on the blood pressures of 853 men and 128 women more than fifty years of age. In the men the average systolic pressure increased from 132 mm. at fifty to fifty-four years of age to 157 mm. at eighty-five to eighty-nine years of age. The systolic pressure of the women increased from 155 mm at fifty to fifty-four years of age to 176 mm. at eighty to eighty-four years of age. The diastolic pressure changed only slightly with increasing age in both men and women.

Sex: It seems obvious that sex is one of the most important modifying factors in blood pressure. First, it should be noted that before puberty there is no sexual difference in systolic pressure. With the development of the gonads, the pressure of boys increases rapidly, so that by the age of eighteen years their mean and modal pressures are about 10 mm. higher than those of girls. Figures supplied by Alvarez[7] show that after the fall in the mean and modal pressure which takes place after the age of eighteen years, there is a rise which appears first in women, and which is also more abrupt than in men. As a result, some groups of data[7,76] show that at the

age of forty years the line representing the mean pressure in women crosses the corresponding line for men.

A number of investigators have found that in the later years of life women tend to have higher pressures than men. It is interesting to note that the two striking divergencies in mean pressure in the two sexes take place at puberty and about the time of the menopause. Alvarez and Zimmermann[7] have shown also that pressures tend to be higher in women who, fairly early in life, show signs of defective pelvic organs. Alvarez believes that a tendency to hypertension, which is probably inherited by both sexes, can, for many years, be submerged in the women of a family if their ovaries function normally.

Range of Normal: The most pertinent question in any consideration of blood pressure is that concerning the range of normal Although several fairly well-controlled studies have been carried out in recent years, no satisfactory standard for the range of normal blood pressure at different ages has been devised.

Alvarez and Stanley after analyzing distribution curves of blood pressure for a large group concluded that the lower limit of normal for systolic pressures must be about 90 mm. whereas the upper limit is about 140 mm.

Robinson and Brucer[74b] made a statistical study of the blood pressures of 11,383 persons in 1939. After eliminating all readings of more than 140 mm. as indicative of hypertension, they concluded that the normal range of systolic pressure for men and women is from 90 to 120 mm. and of diastolic pressure from 60 to 80 mm. They studied also a small group of 500 persons whose blood pressures had been recorded annually for about ten years. They concluded that persons whose systolic pressures were less than 120 mm. tended not to show much variation in blood pressure whereas those who had high readings had much greater variation.

Hines[38b] reported the results of a follow-up study of 1522 patients in which the incidence of the subsequent development of hypertension was correlated with the initial reading of blood pressure. It was found that in the group of patients who had a systolic pressure of more than 140 mm. but a diastolic pressure of less than 85 mm. none had subsequent hypertension. Transient elevation of the systolic pressure to more than 140 mm. and of the diastolic pressure to more than 85 mm. was indicative of a high incidence of hypertension subsequently. A diastolic reading of 85 mm. marked a critical level with respect to future hypertension.

Levy, White, Stroud, and Hillman[59a] analyzed the records of 22,741 officers of the United States Army. The incidence of sustained hypertension tended to be great among those who had transient hypertension at an earlier age and this group also had higher rates for retirement and for death with cardiovascular-renal diseases. No detailed correlation was made in this study in regard to the incidence of the subsequent development of hypertension and the different ranges of initial blood pressure considered to be within the normal range. They considered all levels of transient hypertension, both systolic and diastolic, to be significant.

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L. LEWIS PENNOCK, M.D.

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Low Arterial Pressure

Present Status: Today, just as the mercury column in the thermometer indicates normal, subnormal temperature, and fever, so does the mercury column in the sphygmomanometer indicate normal, low, and high arterial pressure. Regardless of the frequency with which either phase is met in health or disease, the total medical knowledge remains inadequate until all three phases are understood.

Values for normal pressure are now established and the significance of high arterial pressure is generally appreciated. There is today also a plenitude of clinical facts concerning low arterial pressure, but what is still needed is correlation and evaluation of this knowledge. When that is fully accomplished, it may be that a master key will be found and the cause of abnormal variations in health and disease will be uncovered. Once a basis for this functional abnormality is revealed, many perplexing problems in medicine will be solved for physician and patient

The proper placement of any phase or symptom in human disease is of really great importance. *If low arterial pressure is discussed as though it were a disease entity, then the practitioner of medicine will treat it as such. Fortunately, this viewpoint never became established.* Arterial pressure variations should, therefore, be regarded either as evidences of altered physiological functions or as pathological functions.

Arterial pressure indicates the kinetic energy within the artery, and it indicates relatively the pressure within the circulatory system. Low arterial pressure is a characteristic finding in certain types of apparently healthy individuals; it occurs under varying conditions of health and disease. Some clinicians believe that low arterial pressure does not occur in normal health.

Since, up to the present time, there is no final agreement concerning the etiology of low arterial pressure, clinical analysis and synthesis goes on. That which is known seems to point to a definite underlying cause, otherwise how are the many unrelated diseases and abnormal conditions in which low pressure is found to be explained?

Definition: Common experience among clinicians has led to the consensus that a systolic pressure of 110 mm. Hg or lower, when found in the adult human, may be regarded as low arterial pressure. While this is an arbitrary ruling, valid objections have not been raised against it, and 110 mm. Hg is the generally accepted level at which low arterial pressure begins.

Low diastolic pressure values have not come into the calculation because changes in its level seem comparatively insignificant. Pulse pressure changes in this, as well as in many other conditions, have likewise proved to be without well-defined clinical significance.[1]

A certain number of individuals will be found with low arterial pressure who seem normally adapted to the world in which they live. *In this sense, low arterial pressure exists both in health and disease. There are men and women with low pressures who seem to live and work and play without disturbance of health.* It is true that the clinician may discern certain evidences suggesting constitutional inferiority in these people, but the individual may not be aware of inadequate health. If he thinks about it at all, he considers himself as being of a different type, with certain inherent physical limitations; but aside from that, he may feel well and under ordinary conditions he is well. The medical observer often wonders how such individuals work as efficiently and as arduously as many of them do.

The circulatory factors which determine low arterial pressure are presumably the same as those which are responsible for blood pressure as a whole. Physiology has defined arterial pressure as being dependent upon energy of the heart and resistance offered by the peripheral circulation. Total volume of the blood, its physical properties, and elasticity of the blood vessels are likewise important factors. From the standpoint of the clinician, respiratory function and body movement should also be considered as forces of major importance.

Physiological Considerations. ***Adaptability of Forces in the Circulation:*** One fact always to be kept in mind is that the circulation is maintained by three active forces of which the systolic pressure, diastolic pressure, and rate of the pulse are the outward manifestations. It is equally important to recognize that these three forces normally act in unison by reciprocating to each other. Thus it is when systolic pressure falls, diastolic pressure and pulse rate tend to rise. When diastolic pressure rises, systolic pressure automatically tends to recede and pulse rate slows. When both systolic and diastolic pressures rise, the pulse rate tends to fall. This adjustment occurs in health and in disease, every minute of the day, and if for any reason this adjustment cannot be made, strain and a breakdown sooner or later will follow. Thus it is that this triad is constantly at work and should be considered as inseparable values.

The purpose of this constant adjustment is of course the maintenance of cardiac output and blood flow throughout the twenty-four hours, under all conditions and in response to the physiological needs of the organism. It is noteworthy that these changes are actually accomplished within a total variation of less than ten per cent. Thus the changing needs of the organism due to posture, digestion, respiration, chemical and nervous stimuli are met to maintain a constant physiologic equilibrium of the organism.

The blood pressure readings record these variations. The patient who has somehow learned the level of his blood pressure and insists on knowing what the findings are, may fail to understand the meaning of this

physiological variation and may come to look upon the whole procedure with askance. A well known columnist of the day told the story of his visit to a doctor in the morning who told him that the source of his symptoms was low blood pressure. This worried him so much that later in the day he sought another physician who, after taking his blood pressure, said to him: "The trouble with you is that your blood pressure is too high." Whereupon the poor man cried unto himself: "A plague on both your houses"; and on the following day filled a newspaper column with his opinions about patients, doctors, and blood pressure readings. What to him was a demoralizing jigsaw puzzle had the elements of truth but these truths were not put together for him in an understandable way. He should have been told that his nervousness and his anxiety or any other physiological adaptation will produce such variations in blood pressure in one day and that it is Nature's business to do so or else he would soon be in trouble.

Etiology: The impelling question that arises at this point is this Why is it that in two human beings, living under exactly the same conditions, subjected to the same atmospheric pressure of 6 8 kg. per 6 45 sq cm. (15 lb per square inch) on all sides, controlled by the same chemical and biophysical forces, one is found with an arterial systolic pressure of 200 mm. Hg and the other carries a pressure of only 100 mm. Hg? Is this fact in any way comparable to the working of a high pressure and low pressure engine in the field of mechanics and physics? Is the explanation to be found in something like the ratios of narrow bore and long stroke of the high pressure engine as compared to the wide bore and shorter stroke of the low pressure engine? Is it perhaps in the character and quality of the fuel or the air-oxygen mixture? Or after all, will the complete answer be found in the type of engine plus the quality of the fuel plus the amount of available oxygen? This analogy may seem very crude until we review the available facts concerning low arterial pressure and then we suddenly realize the counterpart in each of these two mechanisms and their similarity, as will be seen in the latter part of this discussion.

Gasoline Engine	*Comparable to*	*Cardiovascular System*
Narrow bore + long stroke = high compression	comparable to	vasoconstriction = high arterial pressure
Wide bore + shorter stroke = low compression	comparable to	vasodilatation = low arterial pressure
Gasoline + normal air and oxygen = normal power	comparable to	glucose + oxygen = normal energy
Gasoline + air and more oxygen = greater power	comparable to	glucose + more oxygen = more energy
Gasoline + less oxygen = reduced power	comparable to	glucose + less oxygen = less energy
Gasoline + ethyl + oxygen = maximum power	comparable to	glucose + hormone + oxygen = maximum energy

Incidence. ***In Health:*** The incidence of low arterial pressure in groups of healthy people shows a surprising constancy. Extensive observations

reveal the fact that in a cross-section of population at the ages of seventeen to thirty, the incidence of low arterial pressure was found to be about 3.5 per cent, varying within the limits of 1.8 to 6 per cent.[2] These values have been obtained in students, army recruits, and similar groups.[39,40] They are, therefore, assumed to be true for the general population at those ages. On the other hand, a group of apparently healthy bank clerks at similar ages, coming out of the same general population, showed a striking difference. *In this special group, thirty-eight per cent of males and fifty-five* per cent of females had a blood pressure of 110 mm. Hg or less.

This is most interesting. One explanation is that the individual with a constitutional tendency to low arterial pressure, unable or unwilling to cope with the rugged issues of life, desires seclusion and protection. Knowing that these conditions can be obtained within the walls of the counting house, he or she gravitates to such an occupation. Once there, the limited space in which they spend the day, limitation of muscular and respiratory movement, added to an already existing tendency, produce the final striking result.

TABLE 1

INCIDENCE OF LOW ARTERIAL PRESSURE IN VARIOUS GROUPS

Class	*Number Examined*	*Arterial Pressure 110 or Less*	*Incidence Per Cent*	*Author*
Students, male	656	30 cases	4 0	Barach and Marks
Students, male	1100	24 cases	2.1	Barach and Marks
Recruits (31,596) male	1315	73 cases	5 6	Barach
Recruits (27,224) male	1016	24 cases	2.3	Barach
Aviators, male	1000	18 cases	1 8	Harris
Students, male	6000	132 cases	2 2	Alvarez
Bank clerks, male	*108*	*41 cases*	38 0	Barach
Bank clerks, female	169	94 cases	55 0	Barach

Of course the level of 110 mm. Hg or less has been arbitrarily chosen as the beginning of low arterial pressure. We have accepted that level here largely because of usage by the medical profession as a whole, in order that we may all be speaking in the same terms and to avoid confusion. There is much justification in saying that since a level of 110 mm. Hg is compatible with apparent good health, we should adopt 100 mm. Hg as the level of low pressure, but this would throw out of consideration a great deal of work and data that have been accumulated over the past half century.[38] The clinician is well aware of the element of relativity here and allows for this in his interpretation and evaluation of the patient and his disease.

In Disease: In a previously healthy individual, when low arterial pressure is brought on by disease, it is assumed to be due to the cardiovascular depressant action of that disease. In an individual bordering on low arterial pressure, the cause may even be a minor one.

The following tabulation suggests the various physiological and pathological states in which low arterial pressure is encountered and the conditions which tend to produce it.

In Health:

Infancy.
Childhood.
Adult, constitutional type.
Racial tendency.
Geographic location.
Climate.
Atmospheric conditions.
Body weight.
Body build
Exercise.
Posture.
Respiratory system
Heart.
Blood vessels, capillaries
Autonomic nervous system
Blood loss in donors

In Disease:

Constitutional diatheses.
Disorders of respiratory system.
Disorders of heart.
Disorders of blood vessels
Disorders of blood:
  Chemical.
  Physical.
  Morphological.
Endocrine system (hypoadrenia).
Disorders of nutrition:
  Diabetes (uncomplicated).
  Deficiencies (Beriberi).
  Cachexias
Physical and nervous exhaustion, depressive states
Shock.
  Medical
  Surgical (hemorrhage)
Acute infectious diseases.
Chronic infections
  Focal
  Tuberculous
  Syphilis.
Acute intoxications:
  Chemical agents (arsenic)[52]
  Food poisoning
  Drugs

Clinical Grouping of Cases: In a group of 1865 ambulatory general medical cases in private practice, 253 showed low arterial pressure. This is about four times as many as would be found in a similar sized group of well people, as our previous findings indicated

Some allowance must be made for the accompanying classification of these cases. Individual experience and diagnostic acumen might lead one worker to place a case in one group, while another might place the same patient in one of the other groups. This is particularly true of the constitutional, endocrine, and chronic infection type of case.

In the reports of various writers on this subject, it is clear that associated disease incidence varies with geographic location in which the observations were made, whether the patients were ambulatory or hospitalized, and the type of case likely to consult the physician who made the reports.

Symptoms: The symptoms in patients classified as low arterial pressure vary with the intelligence and psychologic background of the individual. A list of the patients' complaints may be as unrealistic as answers to a questionnaire. In some instances, the patient becomes an artist for the time being, painting a picture for the doctor's benefit. Some of these pictures are drab and foggy, while others are done in gorgeous and flamboyant colors. The physician on guard will separate the wheat from the chaff and give heed only to those symptoms which have true clinical significance.

TABLE 2

253 Cases of Low Arterial Pressure

Clinical Classification	*Cases*
Constitutional types, including asthenics	81
Endocrine types	60
Chronic infections, known localizations	49
Constitutional types, with marked gastrointestinal symptoms	29
Blood dyscrasias	11
Bronchial asthma	9
Cardiovascular renal disease	8
Carcinoma	4
Lues, secondary	1
Psoriasis	1

The 3 5 per cent of humanity with essential low pressure are, of course, in the front line of attack. When unfavorable conditions arise they will be the first to show symptoms. Whatever the strain, after it is set in full motion, symptoms appear which may manifest themselves in any organ or system of organs in the body. The symptoms may be localized or general. The commonest of all complaints is loss of their former sense of well-being; and this is accompanied by early fatigue and physical exhaustion. At times, they have dizziness and motor instability. Symptoms referable to the mental and nervous systems are apprehension, fears, nervousness, insomnia, inability to concentrate, often on anything but themselves, inattention, and headache. Some complain of tinnitus aurium and neuralgic pains, others have intermittent abdominal pains; they complain of arms and legs going to sleep and paresthesias.

Precordial pains, at times indistinguishable from true anginal pains, are a source of anxiety to patient and doctor. They are apt to come on after the patient has done more than he should; after taxation by physical or mental strain; after overeating, drinking, smoking, constipation, or any other stress. It is stress and strain of any kind that these patients cannot tolerate.

Frequently this is the type of patient who says he is at his best toward evening, when the normal man and woman begins to notice the fatigue of the day. These patients will go out to dinner, where they are likely to overeat and smoke and take liquor and gather a good deal of momentum in the course of the evening. By bedtime they are wide awake, and when they finally do get to bed, they are apt to be sleepless for two or three hours. If they do fall asleep, they are apt to awaken at 3 or 4 A. M. and remain wide awake. These patients are sensitive to coffee and to tobacco. Often they become addicted to the use of sedatives and somnifacients which leave them with mental depression and in a daze the following morning. In some instances the patient experiences marked unsteadiness of gait after the use of such drugs. In most instances more harm than good comes from their use. Some have spastic constipation for which they

take laxatives of one kind or another daily, and this hypercatharsis may also be a cause of dizziness or giddiness to the point of disturbed locomotion. In the morning the rested individual is ready for a day's work, but the patient with low arterial pressure is only too often jaded and unfit for the coming day. Thus a vicious cycle is established which keeps them in a state of misery and semi-invalidism from which many cannot extricate themselves.

It should be remembered that these patients are not continuously in this low state. They have periods of well-being which alternate with periods of depression. During the depressed states the blood pressure reaches its lowest levels. Whether a temporary fall in pressure is the cause of the entire episode or is only a part of it, is not so easily determined; that they do occur simultaneously is a common observation.

Referable to the cardiovascular system are precordial pains, dizziness, palpitation, faintness, and syncope. Referable to the digestive system are *indigestion, abdominal discomfort from "gas" in the stomach or intestines*, spasticity, and mucous colitis with its accompanying symptoms. Such are the usual complaints of the patient with low arterial pressure.

The subject of precordial pains, or the "heart pains," of these patients deserves special consideration. While it is often necessary to encourage them and allay their fears, there are times when the doctor is not as sure of himself as he would like to be, in telling the patient that his chest pains are not of cardiac origin. Not infrequently pains occur over the right chest as the counterpart of heart pains over the left precordial area; and this is welcomed by patient and doctor as evidence that the same kind of pain over the heart area is not necessarily of cardiac origin.

In the light of studies and observations in the so-called functional cases and in patients with low arterial pressure, one should not deny too positively the meaning and import of these recurring pains. In fact, clinical experience has taught that the chest pains of neurotic patients should be studied just as carefully as other patients, because some of them will surely end up with coronary occlusions or cardiovascular failure Here, electrocardiographic studies are of prime importance.

Low Arterial Pressure from the Standpoint of the Human Constitution: Without a systematic grouping of the facts, the entire subject of low arterial pressure is a confused mass of disconnected observations leading nowhere. It is in good order, therefore, to subdivide and arrange the available data in such a way that it will have more meaning and lead toward a better understanding. For this, the panel arrangement of Draper,[3] as applied in the study of the "Human Constitution," serves admirably.

Anatomical and Pathoanatomical Panel: *Age:* Infancy to old age is accompanied by a gradual rise in arterial pressure. Observations indicate that pressure levels tend to change at the epochal periods of life; puberty, maturity, and menopause

Sex: From puberty onward, when comparable groups are studied, arterial pressure is found lower in the female than in the male. It is also true that the woman with disease involving her sex organs, will frequently have

higher arterial pressure than the woman with normal organs and sex characters. This was observed by Barach,[2] Alvarez,[4] and others.

Body Weight and Body Build: Most individuals with low arterial pressure are underweight. Reports of medical examiners for life insurance and those of many other observers indicate that this is a general rule.



FIGURE 1 Hyposthenic type, hypotension, sixty-eight per cent (Barach· Arch Int Med)

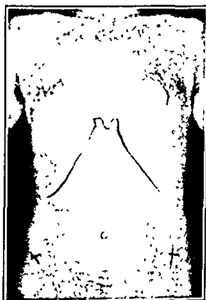


FIGURE 2. Sthenic type; hypotension, 9 7 per cent. (Barach· Arch Int. Med)

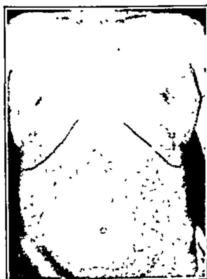


FIGURE 3 Hypersthenic type (Barach: Arch. Int. Med.)

Our observations on 129 cases of low arterial pressure reveal that the body weight of these individuals as compared to the normal standards for age, height, and weight, was decidedly lower than the average normals Of these 129 cases, 105 were underweight, varying from 0.9 to 25 4 kg. (2 to 56 lb.). Twenty-two were overweight, varying from 1 8 to 37 2 kg (4 to 82 lb) and two were of normal average weight. Thus eighty-one per cent of our cases were underweight and seventeen per cent were overweight.

It is not an uncommon experience to find a systolic pressure of 90 mm. Hg in a man 1.9 meters (6 feet, 3 inches) in height Underweight may be said to be a characteristic of the typus hyposthenicus,[2] and no doubt undernutrition, as in the case of the bank clerk, is a contributory factor in the persistently low arterial pressure case.

Well-proportioned women show a blood pressure average of 10 mm. Hg higher than thin women.[5] On the other hand, there is a group of endocrine females with low arterial pressure who frequently are overweight.

By classifying individuals as hyposthenic, sthenic, and hypersthenic, it was found that those with low arterial pressures definitely belong to the hyposthenic type. Occasionally, an individual of the hypersthenic type is found with low arterial pressure, but they are the exceptions. Mistaking the obese for the hypersthenic must be guarded against. A normal chest may be so covered with layers and pads of fat that it has the outward appearance of the hypersthenic; whereas in the latter, it is the bony framework of the thorax and its wide and deep contour which produce the characteristic chestiness.

TABLE 3

PULSE RATE IN 140 CASES OF LOW ARTERIAL PRESSURE

Number Cases	*Pulse Rate*
34	90 to 110
54	80 to 90
52	60 to 80

Respiratory System: The respiratory system in the hyposthenic of the constitutional type, shows a state of development in keeping with the shape of the thorax. The reduced vital capacity of these individuals indicates that the respiratory function is of a lower order of efficiency. Uncomplicated asthma, particularly in younger patients, is frequently accompanied by low arterial pressure. It is also in order here to mention the fact that in patients with dyspnea on exertion and cardiac decompensation, vital capacity is lower than normal. Where there is both diminished vital capacity and a failing heart, low or a falling arterial pressure is the rule.

Cardiovascular System—Heart: There are more normal or slow pulse rates than fast ones in individuals with low arterial pressure (Table 3).

Physical examination and x-ray studies reveal the fact that the constitutional types with low pressure have a narrower and longer heart than the normal. The gourd-shaped heart is part of the slender build of the hyposthenic. It is the type of heart found with enteroptosis, in the tuberculous, and not infrequently in the coal miner with silicosis. In cases of low or falling arterial pressures other than that of the constitutional type, integrity and functional capacity of the heart and blood vessels determine the level to which arterial pressure descends. Where the myocardium or aorta is diseased, low arterial pressure should make one apprehensive of a possible sudden fatality.

Vascular System: The normal or abnormal artery, capillary or vein, and the degree of fibrosis in the vessel, determines its elasticity, distensibility and contractility; all are important factors in determining arterial pressure level. It should be recalled here that only half the cases of arteriosclerosis show high arterial pressure, and that in arteriosclerosis without high arterial pressure, or where the arterial pressure is low, the work of the ventricle is not increased.[6] A strikingly low level of arterial pressure in one arm may be found in the patient who has a relatively normal level of pressure in the opposite arm. This will be noted in coarctation of the aorta, which also will be accompanied by low arterial pressure in the legs. Unilateral low readings may be present in aortic aneurysms, depending upon the site of the aneurysm.

Physiological and Pathophysiological Panel: *Respiratory System:* There are many relations between respiratory function and arterial pressure. As already suggested in the preceding paragraphs, it in inevitable that the underdeveloped and hyposthenic thorax should produce deficient functioning of the respiratory system. Diminished oxygen supply, whether it is brought about in ascending high altitudes, whether it is produced in a closed chamber with gradual reduction of oxygen, or replacement of the normal amount of oxygen by carbon dioxide, carbon monoxide,[7] or any other gas; whatever be the mode of producing anoxemia, fall of arterial pressure is the inevitable result. There are, of course, innumerable ways of producing anoxemia. It may be the result of alterations in the environment or in the living being itself; it may be exogenous or endogenous in origin. Thus, any function or any organ of the body may, directly or indirectly, take part in production of low arterial pressure.

Oxygen and Capillary Circulation: Experimental evidence concerning the part played by oxygen as a cause of capillary contraction, and the part played by anoxemia in producing dilatation is too voluminous to quote. The work of Meyer, in 1906, and of Rothlin, in 1920, has been repeated and substantiated by many physiologists.

Rothlin[9] has shown that in Ringer's solution without added oxygen, the isolated vessel is completely relaxed, while in Ringer's solution through which oxygen is being passed, the vessel attains irritability and contracts directly in proportion to the amount of available oxygen. This contraction phase happens even after a relatively long latent period.

Oxygen effect occurs irrespective of nervous influences responsible for vasoconstriction and dilatation, and irrespective of other chemical or biochemical vasoconstricting substances in the blood.

Thus it is that anoxia is a factor in shock. Low oxygen supply, paralysis of capillaries, diminished blood flow, falling blood pressure, which, after reaching a systolic level of 80, becomes inadequate to carry on the circulation and after that, the manifestations of shock appear.

Of great significance in this connection is the work of the staff of the United States Bureau of Mines at Pittsburgh in their studies on respiratory anoxemia.[7]

Chornyak and Sayers[10] found that when inspired air is poor in oxygen, or in asphyxia, altered circulation, particularly vascular dilatation and stasis invariably follow. When asphyxia is induced by carbon monoxide, there is actual edema of the dorsal motor nucleus of the vagus and adjacent areas in the medulla oblongata and consequent respiratory failure. Taken as a whole, their findings clearly indicate that inefficient respiratory function and insufficient oxidation lead to dilatation of the capillaries. Dilatation leads to fall in capillary and vascular pressure and then to low arterial pressure. Accumulating evidences, both in the clinic and laboratory, thus point to a direct relationship between oxygen, anoxemia, capillary dilatation, and low arterial pressure. Many years ago, Greene and Gilbert[11] showed that low oxygen tension causes a depression of cardiac function.

Atmospheric pressure changes and heat have their effect on arterial pressure.[12]

Heart: Physiologic disturbances of the heart, the arrhythmias *per se*, cause slight or transient lowering of pressure. Their effect on arterial pressure is proportionate to duration and severity of the irregularity. The accompanying myocardial factor in these cases is of greater importance. Pulsus alternans with low arterial pressure indicates grave myocardial damage.

Nervous System: The autonomic nervous system is a factor in low arterial pressure. It is governed by certain higher centers and, in turn, it controls various functions along the lines of its distribution. The patient with postural hypotension is one who has in a large measure lost his reflex vasoconstriction which is necessary to overcome a fall in arterial pressure. This occurs in disease of the sympathetic nervous system, whether it be of peripheral or central origin. There is a transient period of low arterial pressure after the giving of blood, as seen in donors. The severity and frequency of symptoms vary directly with the blood loss. It is interesting to note that saline solution administered before the bleeding will reduce or preclude the episodes of fainting. This was the experience of many workers in England during the blitz in World War II. The studies of Ellis and Haynes[13] point to the brain as a probable center of control. Of the parasympathetic and sympathetic system, the latter is probably more important, influencing blood pressure through its excitatory and inhibitory effects on glands of internal secretion.

Shock: This need not be discussed here, other than to mention that blood pressure reaches its lowest level in shock and in syncope. In shock, the fall in pressure comes suddenly, whether its cause is biochemical, physical, or psychic.

Blood—Anemia: Anemia may be accompanied by low arterial pressure, both happening in the same patient. Whether it be acute anemia due to sudden loss of blood, or chronic anemia from protracted bleeding, or slow blood destruction, the arterial pressure level is found at times to correspond to the blood picture.

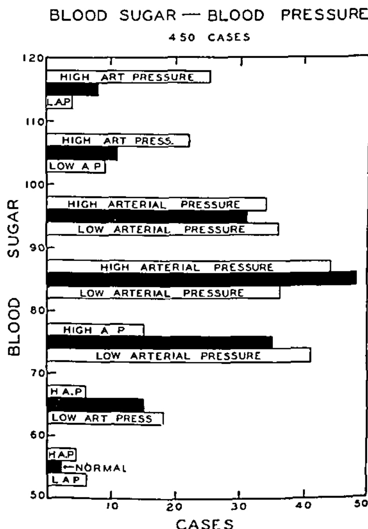


FIGURE 4 Blood sugar and blood pressure—450 cases

A study of the blood in a group of 139 cases of low arterial pressure reveals that seventy-eight per cent of this series had less than 5,000,000 red cells, that fifty-two per cent showed hemoglobin under seventy per cent and that eighty-nine per cent showed a polynuclear count varying between fifty and seventy per cent, and only eight per cent had a polynuclear count of seventy-five per cent or over. This blood picture serves as an index to the quality of the patient's tissues. We have in this, suggestions of secondary anemia and a low polynuclear count which is consonant with the general appearance and state of health of these patients.

Blood Sugar: In 1934, the writer[14] called attention to the observation that patients with low arterial pressure have a lower than average normal blood sugar. Continued studies have verified these findings and have added to the significance of this observation in patients with low arterial pressure. It was first pointed out that in twenty-four out of twenty-five patients, with low arterial pressure the blood sugar was under 110 mg., 3½ hours after breakfast. The present studies include a series of 150 cases of low arterial pressure and a similar number of cases with normal and high arterial pressure. As chart (Fig 4) clearly shows, the low pressure groups were the ones in which the lowest blood sugars were found, and as the blood sugar reached higher levels, the arterial pressures were found to be at the normal or above normal levels

Sodium and Chloride Metabolism: To what extent is the sodium and chloride metabolism involved in arterial pressure? Numerous studies have been made in hypertension, and for many years the salt-free or low salt diet has been considered an inherent part of the proper treatment of the hypertensive patient. *Looking back on the entire experience at the present time, it must be admitted that in most cases little of real therapeutic worth has been added to the patient's well-being by a strict salt control.* Nevertheless, the elimination of salt from the diet certainly does produce a physiological effect. While it may not be said that striking effects are seen in all cases, yet it must be noted that in some the circulatory and systemic effects are very pronounced. How much of this is due to sodium and its capacity for increasing water retention is yet to be determined. Since reintroduction of the rice diet with its minimal sodium, low fat and vegetable protein content, the entire question has been opened up anew and is being studied clinically. The rice diet at this time has not yet fulfilled the hopes of the patient with high arterial pressure

Endocrines: What relationship, if any, do we find between the low arterial pressure phase and the endocrine phase in these patients and are they interdependent or are they merely coincidental? A review of the cases in this series of 253 patients with low arterial pressure which are classified as belonging to the endocrine group, reveals some interesting findings. First of all, sixty-one per cent of the endocrine series were clinical cases of gonadal disturbance or gonadal insufficiency Here we found young people with obesity, suggestive of pituitary disturbance. There were cases of cryptorchidism, adnormalities in the external sex characters, and there were clear cut cases of functional hypogonadism, indicated by sex infantilism in the male and various evidences of hypo-ovarianism in the female. Hypothyroidism following thyroidectomy and cases of diagnosed hypoadrenia were also present in the group

Flippin and Smith[15] reported seven cases of Addison's disease in Negroes, in addition to seven cases previously reported by others Eleven of these came to autopsy and all of them revealed tuberculosis of the adrenal glands. All the cases in which the level of blood pressure was recorded, had low arterial pressure of a marked degree.

Since the clinical syndrome of the various endocrine disturbances are, in many cases, multiple in character representing not an individual glandu-

lar disturbance, it is just as well at this stage of our knowledge to consider them as composite examples rather than instances of specific gland disturbances.

Other Physiological and Pathophysiological Functions: Exertion, fatigue, and physical exhaustion have their influence upon arterial pressure. Every individual, quiet or resting, attains a basal level which is normal for him. There is a diurnal variation as well. During muscular effort, blood pressures rise in proportion to severity and duration of the effort and the fitness of the individual. This rise continues for a variable period and is followed by recession to a subnormal level, which continues for a time. As restitution occurs, the blood pressure again rises to normal.

Posture: Change of posture is accompanied by alteration in systolic and diastolic pressure and pulse rate.[16] These adjust themselves in a short time. Those with poor musculature and low vasomotor tone do not respond as promptly nor in the same way as those who are physically fit. A healthy man put to bed will have a fall in arterial pressure, which will return to normal as he resumes his normal activity.

Orthostatic or Postural Hypotension: This has been described as a clinical syndrome during the past few years, although it was first delineated by Bradbury and Eggleston,[17] in 1925. Time will tell whether this condition really deserves to be considered as a clinical entity and whether postural hypotension will find a place in the nosography of medicine.[41,42,45]

As reports on these cases make their appearance in medical literature, the clinical components of this syndrome are described as (1) a fall of systolic pressure to the point of syncope when the patient assumes the erect posture, the patient being comfortable in the horizontal posture only; (2) an inability to sweat and greater discomfort during the summer months; (3) slow and unchanging pulse rate with change from horizontal to erect posture; (4) low basal metabolic rate; (5) high blood urea and nocturnal polyuria; (6) evidences of pathology in the central nervous system and apotentia.

The pathologic physiology of this condition appears to be a failure of the sympathetic nervous system which normally controls vasoconstriction, acceleration of the pulse, sweating, gonads, etc.[13] Of special interest to the writer is the nocturnal polyuria which was almost invariably present in the reported cases. Clinical studies have shown that while nocturnal polyuria is ordinarily found in the hypertensive-nephritic group of cases, it also occurs in patients with low arterial pressure.[18] Those studies revealed that the causative factor in nocturnal polyuria was circulatory and that it was induced by slowing of the pulse, prolongation of the diastolic phase, and alteration in the pulse pressure during the hours of sleep; all of which led to the filtration of more water through the kidneys. Urea and chlorides in the blood content and urinary output revealed no constancy in either direction.

In the cases of orthostatic or postural hypotension studied and treated thus far, as reported by the various writers,[19,20,21,22] best results were obtained by the use of ephedrine sulfate, benzedrine sulfate and neosynephrine hydrochloride. Of these, the latter seems to have been most effective.

Postural (Orthostatic) Hypotension in Diabetic Neuropathy Rundles[47] describes cases of orthostatic hypotension in diabetic neuropathy characterized by certain clinical manifestations. In these patients there are evidences of involvement of the peripheral autonomic nerves with resulting orthostatic hypotension and orthostatic tachycardia with lack of the normal reflex cardiac acceleration. The clinical manifestations in these patients are dizziness, faintness, syncope, generalized coldness due to impaired regulation of body temperature, or generalized sweating. Some have chronic diarrhea, neurogenic bladder paralysis, impotence, and in others there is edema of the lower extremities. This syndrome not frequently occurs in patients who also have diabetic retinopathy.

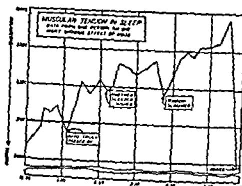


Fig. 5

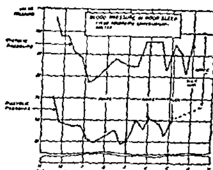


Fig 6

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FIGURE 6. The night on which this test was made was hot and noisy Notice the sudden
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One who sees large numbers of diabetic patients is impressed with the relative frequency of disseminate neuropathic lesions which are not necessarily restricted to the middle aged or elderly diabetics. It is readily understood that the autonomic nervous system may be involved as well as any other nerves. The arch type of this is seen in the so-called tabes diabetica. Experience shows that these symptoms may make their appearance shortly after a severe upset in the course of the diabetes, whether it be an intercurrent infection, diet upset, or diabetic coma.

Sleep: There is a distinct fall of 10 to 12 mm. Hg arterial pressure after the fourth hour of sleep, just as there is in the pulse, respiratory and metabolic rates. During sleep, muscular movement, circulation, and oxidation find their lowest levels of the day.

Kymographic studies made on a group of young Americans at Colgate University[23] re ... in
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corresponding rise and fall in systolic and diastolic pressure and pulse rate, as shown in Figs. 5 and 6. For the majority of young and healthy subjects, the systolic pressure ranges under 100 mm. Hg during sleep.

Race: It is a well established fact that certain people of the East have lower arterial pressure than those of the Occident. In 500 Hindus, McCay[24] reports an average blood pressure varying from 90 to 105 mm. Hg.

Foster[25] has found that Chinese have definitely lower blood pressures than Americans. Of a group of thirty-five Americans residing one year in China, twenty-three showed a definite fall in pressure. Citing a number of specific cases, one fell from 145 and 140 to 128 and 120 mm. Hg; one fell from 140 and 135 to 125 and 108 mm. Hg after two years; one, a woman, from 120 in United States to 88 mm. Hg in China.

An important observation on this point comes from the Sun Life Insurance Company, whose records show that in 1000 policies, the blood pressure values were constantly lower in Chinese than in the white population. It was also noted that there was an absence of symptoms due to low arterial pressure in these cases.

Of the various explanations offered for the low arterial pressure of the Chinese as a people, the following reasons have been proposed from time to time: (1) Lighter weight of the Chinese; (2) smaller stature; (3) lowered muscle tone; (4) racial endocrine differences; (5) low fat, low animal protein and low salt diet; (6) climate and lower vasomotor tone; (7) absence of nervous strain. It should also be noted here that many of the observations on low arterial pressure were made in cities which are not in tropical areas. Peking, for example, is in the same latitude as New York.

Tung[26] has also observed that when Americans take up residence in China, their blood pressure falls to a lower level. In a series of fifty-eight Americans who had lived in China for a year or more, the average fall of systolic pressure was 9 mm. and diastolic pressure 11 mm. Hg. Sixty-four per cent of his series showed this fall. It has likewise been noted that among the poor Chinese, certain African tribes, and in Panamanians, the level of blood pressure does not rise with advancing years as it does in this country and in Europe.

There is a unanimity of opinion that the fall in arterial pressure is not due merely to dilatation of peripheral vessels nor change in diet or personal hygiene. Most writers tend to believe that the important factor resides in the central nervous system and psychic life of the individual. Mental and psychic influences over the innervation of the cardiovascular system, perhaps by way of the endocrine system and metabolism, are believed to be the chief factors.

Interestingly enough, Japanese have a higher level of blood pressure than the Chinese, for they have taken on a more western mode of living, and they have submitted to greater regimentation. It has also been shown that hypertension among urban Japanese is nearly as frequent as in America.[27] *It seems that those people who have not yet been influenced by modern modes of living, those who remain attuned to a quiet life and those who are content with the simplicities of life, may continue to escape the onrushing pressures which are overwhelming modern man.*

The Dean of a School of Medicine in China related to me, some time ago, the vigor and enthusiasm with which he first returns to his work after a leave of absence to America. On his return to China he finds himself moving fast and with a keen desire to get things done as he had been planning them while away. He then notes that those about him do not seem quite so enthusiastic as he would like and that some even look with mild disdain upon his feverishness and desire to do things promptly, in true American fashion. In a little while, however, he notes that he too is slowing up and after four to six months more, he discovers that he has become definitely synchronized and attuned to the tempo of life about him. All of which has brought him to the conclusion that there is something in the entire atmosphere of living in China which induces easement, patience and a lowering of the pressures of life

Climate: Arterial pressure is 10 to 15 mm lower in the tropics. The physician in the subtropical and tropical climates sees more cases of low arterial pressure than one in the northern temperate zone

Occupation: Mode of living and occupation have their influence on level of arterial pressure. The writer has observed that nurses on night duty, after a period of six months or longer, will not infrequently develop low arterial pressure with its accompanying clinical syndrome.

Immunological-Patholmmunological Panel. *Acute Infectious Diseases:* Most acute infections are accompanied by a fall in pressure. It is this lowering of arterial pressure from the very onset of the disease that makes standing or walking difficult or impossible and forces the patient to bed, and that is perhaps the main reason why the acute febrile patient falls when he attempts to get out of bed.

TABLE 4

BLOOD PRESSURE IN INFLUENZA

Cases	*1st Day*	*2nd Day*	*3rd Day*	*4th Day*
50	115	92	85	112

Acute Colds: There is a marked fall of arterial pressure in the patient with an "acute cold," at the same time when he is complaining of muscle pains, shivering, cold hands and feet, and general malaise, at the very beginning of these acute illnesses. This is most marked in cases of la grippe and influenza. Arterial pressure reaches its lowest level during the course of epidemic influenza.

Influenza: The writer's studies during influenza epidemics showed that there is a progressive fall of blood pressure from the first to the third day. In favorable cases, on the fourth day the pressure remains the same or begins to rise. In a group of 50 such patients,[10] all had low arterial pressure; the lowest systolic pressure being 72 mm. Hg and the lowest diastolic pressure being 48 mm. Hg.

Pneumonia: In pneumonia, the tendency to low arterial pressure has been to some a constant source of apprehension; so much so, that the

level of arterial pressure was used as a guide in prognosis. It is not a true guide, however. Not infrequently, patients known to be of the constitutional type that have low pressure with its accompanying clinical syndrome, will go through a typical lobar pneumonia with evidence of reserve and with a good recovery, even without a protracted convalescence. When pneumonia develops in one who is fatigued or exhausted from the very beginning of the disease, as often happens, then a low arterial pressure is of serious prognostic significance, and its meaning is comparable to the absence of leukocytosis in the disease. A steady fall in arterial pressure may indicate progressive myocardial failure. In that case resolution is delayed, the lung surrounding the pneumonic area is congested; it shows all the physical signs of moisture and edema that increase from day to day. With this there is marked cyanosis and its usual accompaniments.

The other type of cardiovascular failure in such pneumonias bears the earmarks of vasomotor failure due to the pneumococcic toxemia. This type of patient, overwhelmed by toxemia, will show a falling blood pressure and a rapidly increasing and irregular pulse rate; all of which may terminate speedily even before the lungs become moist or wet and soggy with all the typical physical signs.

TABLE 5

BLOOD PRESSURE IN TYPHOID FEVER

Cases	*1st Week*	*2nd Week*	*3rd Week*	*4th Week*	*5th Week*	*6th Week*
81	93	92	83	83	85	90

Typhoid Fever: Typhoid fever is characterized by low pressure throughout, as was shown by the writer many years ago.[28] Here, arterial pressure descends to a lower level from week to week, as the disease progresses, reaching its lowest level during the fourth week; after which, as the disease abates, the pressure rises with the recovery of the patient.

Trichinosis: Comparable to the low arterial pressure of typhoid fever and influenza is the low level of pressure attained in the acute infectious stage of trichinosis. This was noted by Gruber[29] in 1925 and Cheney[30] in 1926. Reports of recent epidemics by Spink and others verify this. In the epidemic reported by Spink and Augustine,[31] twelve of thirty-five cases had a systolic pressure under 100 mm. Hg and a diastolic pressure as low as 38 mm. Hg. For the group the average diastolic pressure was 50 mm. Hg. An experience of the writer's covering an epidemic of ten cases, two of which were fatal, illustrated this very clearly. With the fever there is profound depression and when one considers the degree to which the entire nervous system may be involved in this disease, it is readily seen how the various circulatory controls can be altered and depressed.

Chronic Infections—Focal Infections: These are frequently found in patients with low arterial pressure. *They may be a contributory depressing factor, but focal infections per se can account only for a small percentage*

of cases. Not infrequently the low pressure disappears with the improvement which follows removal of foci of infection.

Tuberculosis: Low pressure in tuberculosis is very common, often the degree of low pressure is in keeping with the severity of the disease. But, low arterial pressure is not a diagnostic criterion in cases of tuberculosis. If one were to rely too much on the level of arterial pressure in the type of patient in whom tuberculosis is commonly seen, he would make many errors in diagnosis. Various studies have shown that with the patient's general improvement, the level of arterial pressure tends to rise to a higher level.

SYSTOLIC BLOOD PRESSURE
1000 DIABETICS

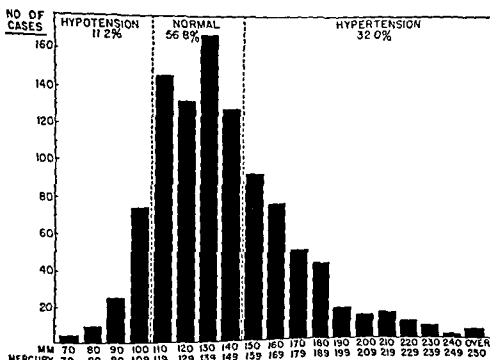


FIGURE 7.

Syphilis: Low arterial pressure, apparently functional in origin, or possibly due to the acute infection, *is not* infrequently seen during the secondary stage of syphilis when the patient is toxic, mentally depressed and discouraged. If and when a *decidedly* low arterial pressure is found later in the disease, in all likelihood such cases will be found to have an organic basis.

Diabetes Mellitus: Diabetes patients show normal, high, or low arterial pressure depending not *only* upon the diabetes, but also on the patient who has the disease. The chart (Fig. 7), *based on a group of* 1000 ... pressure levels in the group. It will be noted

that twelve per cent of the entire group showed low arterial pressure. In part this incidence of low blood pressure is due to the juvenile diabetics included in the series, in whom low arterial pressure is particularly noticeable; first because of their youth and in part due to the sugar loss in this disease. Everyday observations in this disease have led the writer to the conclusion that during the uncontrolled period of diabetes, arterial pressure is lowered and when a normal metabolic state is reestablished, the pressure will return toward the patient's former level. Diabetes with its hyperglycemia and ketosis, when present, lowers the arterial pressure.[48,49]

Low Arterial Pressure and Diabetic Coma: In diabetic coma the level of blood pressure varies directly with the intensity and seriousness of the patient's condition. Experience has shown that both systolic and diastolic pressures fall as the comatose state of the patient advances. The level of systolic pressure is not as significant as the diastolic pressure. An adult in early or mild coma may have a diastolic pressure of 80 mm. Hg. In moderately severe cases the pressure may vary between 80 and 60 mm. In severe cases, the diastolic pressure will range between 60 and 50 mm. Hg. In the profound cases the diastolic pressure will have receded to between 50 and 40 mm. Hg. That low level is found in cases in which the coma has lasted thirty-six hours, where the blood sugar shows little or no response to treatment, where the blood plasma CO_2 is ten volumes per cent or less and when there are other evidences indicating a fatal outcome. When the diastolic pressure reaches 40 or is falling below that level, the patient is dying. Observations in many of our cases of diabetic coma have shown that the diastolic level is the important prognostic factor in the outcome of these cases.

Renal Glycosuria: In one group of twenty-one unquestionable cases of renal glycosuria, thirteen had well defined low arterial pressure, *i. e.*, under 110 mm. Hg. Of the other eight, only one showed a blood pressure over 130 mm. systolic. Thus we have here the association of low blood sugar and low arterial pressure.

THEORIES CONCERNING CAUSATION OF LOW ARTERIAL PRESSURE

The foregoing observations cover much of the material evidences concerning low arterial pressure. When at last an underlying factor common to all these conditions is found, then and only then will the whole problem be understood. Various explanations and hypotheses have, from time to time, been set forth as the cause of low arterial pressure.

Friedlander,[32] while of the opinion that the etiology of low arterial pressure is not yet worked out, believed that loss of vasomotor tone, such as is found in focal and in chronic infections, is the outstanding important factor. He, therefore, proposed the hypothesis of capillary stasis, due to the poisoning effect of histamine or histaminelike bodies.

Dally[33] believed that physical and psychical efficiency depends on vitality of the somatic processes, vitality itself depending on a state of metabolic equilibrium. Disturbances of this equilibrium, which in turn

lead to vasomotor disturbances, produce variations in arterial pressure. These variations lead to higher or lower pressure. With this in mind, Dally postulated his biological law of low arterial pressure. Low arterial pressure, congenital or acquired, temporary or permanent, [illegible] always to be regarded as an expression of low vitality."

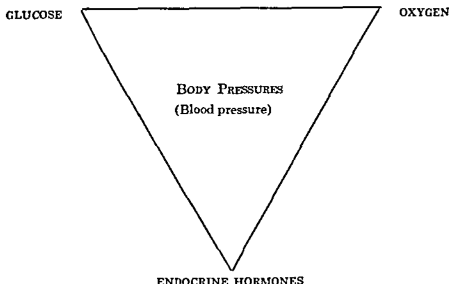
The writer[2] called attention to the fact that *wherever low arterial pressure is found, there are suggestive evidences of lowered respiratory function and diminished oxygenation.* The constitutional or hyposthenic type of individual, the typical patient with low arterial pressure, is slender, undersized, undernourished, nonathletic. He has narrow nostrils, nasal obstructions, a narrow chest, poor and relaxed musculature, drooping shoulders, low vital capacity, shallow and irregular breathing; all of which tend to produce deficient respiratory function and a reduction in the diffusion coefficient of oxygen with lessened oxygenation. Low arterial pressure is most striking in those acute infectious diseases in which the respiratory tract, with its swollen mucous membranes and a reduced permeability to oxygen, is part of the disease. Here the previously normal individual develops low arterial pressure as the direct effect of his disease. Acute infectious diseases of the upper respiratory tract, influenza, typhoid fever with its respiratory complications, pneumonia, and other acute infections are accompanied by a marked fall in pressure. Low arterial pressure is also common in uncomplicated chronic pulmonary disease. In these and in other conditions in which low arterial pressure is found, there are many outward evidences of interference with normal respiratory function and oxygen utilization. Thus oxygen want and disturbed functioning of the circulatory system from the smallest capillaries to the heart proper go hand in hand; where one appears, the other follows.

Glucose—The Fuel of Life: In 1934, the writer[14] first called attention to the occurrence of low blood sugars in cases of low arterial pressure, suggesting its etiological significance. Further observations have confirmed this viewpoint and emphasized its meaning. It is becoming evident that the essential role here is played by oxygen and glucose, and behind these two there probably is the endocrine factor. If present-day conceptions of the pituitary influence over the carbohydrate metabolism or the parts played by the adrenals, thyroid and insulin mechanism prove to be correct, then the endocrine hormones will come to be looked upon as catalytic agents which set off the spark for the metabolism, in the presence of an available supply of glucose and oxygen. Of course, there is always the additional influence of the central nervous system behind all of this as well as other vital functions.

This [illegible]

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low arte[illegible]
organism [illegible]
pathological by-product of a disturbed state of the organism due to some disease.

Prognosis: A glance at the hyposthenic and hypotensive type of individual (Fig. 1) quickly suggests that his physical capacity is greatly



limited. Of fifty-five marathon runners studied in 1909,[34] we found that three had low arterial pressure. Before the race of 40 kilometers (25 miles), our evaluation of their physical condition placed them in forty-third, fiftieth, and fifty-first place. In the race one dropped out in the first few miles, one ran 16 kilometers (10 miles); and the other ran 20 8 kilometers (13 miles) and quit. When it came to a gruelling contest, these hypotensives were completely outclassed.

Harris of Pittsburgh, over a number of years, examined 1000 applicants for aviation pilot license. In studying these records with him, I found that eighteen had low arterial pressure. A follow-up of the eighteen cases revealed that only three turned out to be good pilots. The others were rejected or gave up the work or were killed. Thus we see that the individual with low arterial pressure fails when placed in a position requiring physical stamina, endurance, and above all unerring and quick response in emergencies.

In disease, particularly in pneumonia, an unchanging low arterial pressure is of no decided prognostic value. However, a steadily falling pressure at any stage in the course of pneumonia is of grave import. In tuberculosis a rising pressure comes with improvement. In organic lesions of the heart, aorta or blood vessels with an unusually low or falling arterial pressure, experience has shown that death may occur very suddenly. This does not apply to rheumatic heart disease.

In surgery, an individual with sustained arterial pressure, even if quite low at the beginning, will stand an operation as well as others; but a falling pressure is a danger signal, regardless of the type of anesthesia.

Pepper[35] believes that in a certain proportion of cases there is a relationship between low arterial pressure and cerebral or coronary thrombosis, on the basis of stagnation of blood flow. Applying this clinically, he believes that indiscriminate reduction of hypertension will favor slowing of the flow of blood, thus inviting the occurrence of a thrombus.

It may well be asked, "What is the outlook for the average individual

with low arterial pressure in health or disease?" It is the experience of all who have studied this problem, that *after middle life in the absence of an active disease, subjects with low arterial pressure have a better life expectancy than those with normal or high arterial pressure* The lower energy index of the circulatory system in individuals with low arterial pressure suggests less wear and tear on the circulatory system This lessened wear and tear should be conducive to the longevity which statisticians find in cases of low arterial pressure. It is not that these individuals stand the wear and tear of living better than others More likely is it that their protective reactions to life about them are better developed than those of the average individual who, with a greater abundance of energy, throws himself into the fray of living and exposes himself to excesses and complications. The patient with low arterial pressure may have many symptoms and complaints, but he weathers them as well, and sometimes better, than the individual with normal blood pressure.

The following table is of interest in the prognosis of persons with low arterial pressure.

MORTALITY OF PERSONS WITH LOW BLOOD PRESSURE LEVELS ACCORDING TO VARIOUS INSURANCE COMPANIES

Company	*Blood Pressure Level*	*Mortality*	
		Average Pressure	*Low Pressure*
		Per Cent	*Per Cent*
Northwestern Mutual	100 mm. and under (systolic)	80	33
American Actuarial Society	105 mm and under (systolic)	86	47
	106 and 110 mm (systolic)	86	65
Mutual Life of Canada	10 mm below average (systolic)	100	83
	15 mm below average (systolic)	100	87
Joint Committee on Mortality	5–15 % below average (systolic)	100	94
Prudential Life	Under 70 mm (diastolic)	72	49
New York Life	16–24 % below average (mean pressure)	97	93
	5–15 % below average (mean pressure)	97	91

Treatment: The experienced and wise doctor will succeed in the care and treatment of a patient with low arterial pressure, just as he succeeds in the care and treatment of other patients. When a depressing factor in the patient's health is discovered and removed or corrected, the results will be satisfactory. When the cause is not discoverable, or if the frustration of a patient is beyond medical treatment or advice, the physician's effort will fail. A ruined or a worried and sleepless business man may need

a banker, rather than a doctor, for the exhaustion and psychasthenia which follow his misfortunes.

For those who by their very nature are endowed with low arterial pressure and who under ordinary circumstances are symptom-free, it is well to realize that nothing need be done and still more important is it to know that nothing can be done to alter the level of their arterial pressure. In these cases, fools rush in where angels fear to tread.

On the other hand, when there are subjective and objective clinical symptoms definitely indicating the need for interference by the physician, the most effective treatment is a period of rest, though not necessarily a prolonged one. And most important for morale and recovery, the doctor should not tell the patient or the family that he or she has had a "nervous breakdown." Many doctors who use this term freely do not know what a "nervous breakdown" really is. That term should be reserved for the psychiatrist who has properly evaluated the patient's reactions to frustration and defeat and knows how to deal with them and still do the patient more good than harm. It would be interesting to ask some doctors to discuss this subject before a group of intelligent medical men. It might cure them of the use of a terminology which leaves the patient mentally scarred and fearful, and a ready victim for another "nervous breakdown."

Removal of harmful factors, organic and psychic; physical and mental rest; a normal diet; hydrotherapy and massage; everything that can be done to restore the patient toward a normal state should be instituted. In time, a resurgence of well-being and vitality will become manifest and the patient will be restored to his normal state. It is in this type of case that the average physician has failed utterly to take advantage of the therapeutic value of hydrotherapy and massage. *With massage, with passive and active exercise properly carried out, muscle tone and muscle growth can be increased to a surprising degree, even in men of seventy.*

The physician who is to handle many of these patients will find it necessary to practice both preventive and curative medicine to the full extent of his knowledge and wisdom. The things he will have to do are legion and no attempt will be made at enumerating them here. He should be a votary of eugenic marriages; he should recognize the importance of proper infant feeding, care in childhood, nutrition in child and adult life. He should realize the importance of climate, proper clothing, maintenance of normal body weight; the need for daily physical exertion, sufficient hours of rest, healthy posture; avoidance of those factors which may interfere with normal respiration; avoidance of things and situations which cause cardiac and circulatory strain; avoidance of overtaxation of the nervous system; prevention or removal and cure of infections when possible; avoidance of endogenous or exogenous intoxications; and correction of endocrine disturbances when possible. The physician who recognizes the standards of health will discern deviations from these standards and aim to correct them.

Where there is no specific disease, there is no specific treatment. Medication on the whole has been disappointing. Jeffers, Montgomery, and Burton[44] have aimed at therapeutic results, but such drugs as ampheta-

mine, paredrinol, epinephrine, and ephedrine have been used, without striking benefit.[45,51,54] Experience will prove that the single drug or special method highly recommended at one time will be superseded by another, often in rapid succession. Whatever mode of treatment the attending physician will advise should be planned for the patient with precision. The physician who has faith in the success of his treatment will unconsciously stimulate and encourage the patient to make whatever effort is necessary to give up an unhygienic mode of living and to adopt a better one. In this type of patient, as in many others, the one who lives a disordered existence and seeks cures in a bottle of medicine is on the way to disappointment.

Patients are too seldom impressed with the fact that the so-called everyday advice of the physician is really the crystallization of man's total experience, and that he who will carry out such advice in orthodox fashion is the one who will attain desired results.

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26

Arterial Hypertension

Introduction: The problem of elevated arterial blood pressure will be considered from three of its different aspects· First, the clinical problem as seen at the bedside; second, the problem of its mechanism; and third, the problem of its treatment. Clearly it is not possible in a communication of this nature to present and discuss all of the evidence which is now available, but an attempt will be made to present a more or less unified concept, thus reflecting in large measure, perhaps too large, the views of the author.

Tabulation of the morbid states in which arterial hypertension occurs shows at least fifty-eight of them, bearing eloquent testimony to the complexity of the problem. Most of these states are uncommon or associated causes. Probably Bright's disease and pyelonephritis contribute most to this group. Hypertension, both essential and malignant, in which the origin is conjectural, dwarf by far all other causes. So common is the finding of elevations of arterial blood pressure above the accepted standards of normality, that some have questioned the validity of the standards.[41] Mortality statistics, however, urge caution in raising them to soften the urgency of the problem.

Part of the indecision as to whether elevated blood pressure as an isolated finding is synonymous with essential hypertension rests on the fact that this is insufficient evidence to characterize the disease. During the course of our discussion, evidence from sources other than the blood pressure measurement will be presented, which, in my opinion, further delineates the disease.

Despite the fact that elevated blood pressure is usually due to essential hypertension, it is often rewarding to search for other causes because some of these are remediable. To facilitate this search, I have grouped the various clinical types of hypertension under the headings renal, cerebral, cardiovascular, and endocrine (Table 1). I had in mind no thought of permanent codification but rather to provide a framework on which future knowledge might be systematized and integrated.

It will be noted that no attempt has been made to classify the genetic factors of essential hypertension. Some have attempted to do so, but, unfortunately, diagnostic criteria are inadequate to establish these compartments as disease entities. Contemporary knowledge permits only, with the exception of renal hypertension, the primary diagnosis of essential or malignant hypertension with emphasis on the origin of dominant signs and symptoms as ancillary to them.

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TABLE 1

Classification of Hypertension

Renal:
- (a) Affections of Vessels:
  - Arteriosclerosis
  - Panarteritis nodosa
  - Arteritis
  - Anomaly
  - Obstruction (tumors, aneurysm, arteriosclerosis, embolism, thrombosis)
  - Thromboangiitis obliterans
  - Visceral lupus erythematosus
- (b) Affections of Parenchyma:
  - Acute nephritis
  - Chronic nephritis
  - Pyelonephritis
  - Hydronephrosis
  - Polycystic disease
  - Amyloidosis
  - Infarcts
  - Tumors
  - Hypernephroma
  - Ectopia
  - Toxemia of pregnancy
  - X-ray lesions
  - Renal stones
  - Hypogenesis
  - Dystopia
  - Sarcoid infiltration?
  - Wilms' tumor
- (c) Affections of Perinephric Structures:
  - Perinephritis
  - Tumors
  - Hematoma
  - Retroperitoneal masses causing pressure on parenchyma
- (d) Affections of Ureter:
  - Obstruction (pelvis, ureter, prostate, urethra)
  - Pyelitis

Cerebral:
- Increased intracranial pressure (trauma, tumor, inflammation)
- Diencephalic stimulation
- Anxiety states
- Lesions of brain stem (ascending paralysis, poliomyelitis)
- Porphyria

Cardiovascular:
- Heart failure
- Arteriovenous fistulae
- Angina pectoris
- Heart block
- Coarctation of aorta
- Atheromatosis
- Lead poisoning?
- Polycythemia

Endocrine:
- Chorionepithelioma
- Pheochromocytoma
- Adrenal carcinoma
- Adrenal hyperplasia?
- Cushing's syndrome (pituitary adenoma)
- Pituitary basophilism?
- Acromegaly
- Thymic carcinoma
- Hyperthyroidism
- Arrhenoblastoma
- Toxemia of pregnancy

Unknown:
- Essential hypertension
- Malignant hypertension

A. BEDSIDE OBSERVATIONS

Normal Blood Pressure and Its Relationship to Hypertension: The question of what constitutes normal blood pressure has received the attention of many investigators. The problem is an important one, especially so since the finding of hypertension is confused, I believe, with the diagnosis of essential hypertension itself. Indeed, many physicians make

the diagnosis on the basis of measurement of arterial pressure alone, failing to search for the other signs characteristic of the disease. So it comes about that blood pressure greater than the accepted norm, automatically determines the diagnosis and it is seldom anything but essential hypertension. Thus, it should be emphasized that elevated blood pressure as an isolated finding is not sufficient on which to make a diagnosis. The question of what constitutes normal blood pressure is discussed in a previous section.

Vasomotor Lability: Inherent in this term is no connotation of a diseased vasomotor control. Everyone is familiar with individuals whose blood pressure and heart rate are labile and often do not adjust properly to the needs of the occasion. For example, these persons are often unable to stand for any length of time without transient hypotension, tachycardia, sweating and fatigue. Blood pressure may rise transiently with tachycardia at the thought of the sphygmomanometer. Such patients are often said to be neurotic, as though that provided an explanatory diagnosis. I know of no certain evidence that vasomotor lability with tachycardia is a prodrome of essential hypertension.

Prehypertension: By prehypertension is meant a state in which the blood pressure is periodically slightly elevated above the accepted standards of normal in the absence of obvious causes (such as fright) for this elevation, and which ultimately leads to essential hypertension. The question of the significance of the prehypertensive state is one of very great importance to the clinician, insurance examiners and public health authorities. For this reason, it will be of value to examine some of the evidence bearing on it.

It has been obvious ever since the sphygmomanometer was introduced that variability of arterial pressure was marked, but what constituted normal variability and pathological variability was not so clear. Years ago it was recognized that the occasional finding of elevation of arterial pressure to perhaps 160/100 mm. Hg in young people might be a danger signal. But experience taught that by no means all such persons finally developed essential hypertension. The period of excessive alarm gave way to one of nihilism in which abnormal elevations of blood pressure were brushed aside as of no importance. The contemporary period is one in which an attempt is being made to unify the two views, but there are still many observers at one or the other extreme.

The general view held by physicians who have examined university students is that of those who have systolic pressures above 140, about 15 per cent persist at this level and presumably develop essential hypertension. Diehl, however, found no positive correlation between the height of the blood pressure and its variability, and therefore it seemed unlikely to him, at one time, that transient elevation of arterial pressure in young persons represented the first stages of essential hypertension. In a subsequent paper, 155 students with elevated blood pressure were followed for a period of seven years. Diehl states that young men who show persistent, intermittent, or even transitory elevation of blood pressure during their college years are much more likely to have elevated pressures after a

period of five to ten years than those in whom the blood pressure was consistently normal. In short, the probability of their having hypertension in later years is apparently in direct proportion to the frequency with which their pressures were raised while in college. This change of viewpoint is illustrative of that in many clinicians' minds. At first one tends to ignore slight rises in arterial pressure, but after watching these people for years, the conviction grows that many of them are developing essential hypertension. It is difficult to keep from being swept away on a wave of pessimism, but experience also teaches that some with transiently elevated blood pressure do not develop essential hypertension and tachycardia.

Lee examined a group of 662 young male college students (average age eighteen years) finding the average arterial pressure to be 120/80 mm. Hg. But 13 per cent were over 140 and he wrote that in the absence of other abnormal findings, moderate increase in systolic pressure seemed to be of no significance. Twenty years later he found that a small group of these subjects with previous transitory hypertension had developed well-defined essential hypertension, and one gets the impression that in the light of his greater experience he would view transitory hypertension of definite but poorly delineated significance.

A careful study of 3598 college boys showed that 10 per cent had blood pressures of 140 mm. Hg or greater without abnormalities of the heart or proteinuria. Forty-nine of this group were followed and sixty-six of a control group Twenty-two per cent of the hypertensive group continued to show pressures above 140 after ten years, while only 6 per cent of the control group did so. A history of vasomotor symptoms, *i. e.*, palpitation, sweating, flushing, blushing, and chilly sensations was elicited in 14 per cent of the normotensive group and in 25 per cent of the hypertensive. A positive history of cardiovascular disease was obtained in 20 per cent of the normotensive group and in 24 per cent of the hypertensive.

In a later paper, the same author found that the incidence of transient "nervous hypertension" constitutes 10 to 15 per cent of the male applicants for naval commissions, which is about what would be expected in civilian practice. A family history of vascular disease was elicited in half the applicants with "nervous hypertension" but was definitely more frequent (75 per cent) in patients with essential hypertension. Palmer considers the prognosis of transient "nervous hypertension" as indicated by a long follow-up study of twenty-five cases to be excellent. Indeed, he suggests that this syndrome need not be disqualifying for military service.

Our own experience with nearly 300 of these patients, some studied for twenty-five years, has left little doubt that essential hypertension need not necessarily follow such transient rises in blood pressure. On the other hand, more than the usual number of hypertensives are recruited from their ranks. Unless the more elaborate laboratory and clinical examinations do in fact differentiate between those who will develop it and those who will not, about the only practical way to manage these patients is to give them annual examinations until a trend is established.

As an example of what I believe to be a somewhat extreme view, let me quote from a paper of Robinson and Brucer[60(b)]: "A blood pressure history

of over 120 systolic and 80 diastolic over a ten-year span in a man or woman is pathologic, and is an almost infallible sign of incipient hypertension. Once a pressure is definitely established in this range, it seldom if ever will become normal." In some ways this is a safer view than that which has a ready excuse for arterial pressure obviously elevated. Hines[31] believes that excessive variability is evidence of prehypertensive states but suggests that a patient, regardless of age, whose blood pressure is not elevated as a result of nervous stress to more than 140/85 is unlikely to develop hypertension subsequently. Elevation of systolic pressure alone is of little prognostic value. Hines' figures are impressive Of 1522 patients who originally had pressures 140/85 or above, 82 per cent had developed clinical hypertension after twenty years, while in the group below 140/85, only 3.8 per cent had developed it, and below 110 70, none had. Thus, in this view, variability of blood pressure is important, but the limits rise from 120/80 to 140/85 mm. Hg, a very considerable one in this range. From his experience in the navy, Master[10] would raise the limits of normal blood pressure because hypertension is so common that blood pressure limits, after the age of forty, of 140 90, 150 95, and 150/100 are not considered abnormal by him. He agrees that under the age of forty borderline or hypertensive levels, slight or moderate, whether obtained under stress or not, probably indicate future hypertension, even if normal readings are finally obtained.

We find it useful to divide these people into four groups:

1. Those with ***simple vasomotor lability.*** This group includes individuals who have transient episodes of elevated arterial pressure with tachycardia but without the characteristic clinical picture of essential hypertension. The latter does not necessarily develop.

2. ***Prehypertensives:*** Those who will develop essential hypertension.

3. ***Neurogenic hypertensives:*** Those with established hypertension but on a "neurogenic" basis, *i. e.*, with signs and symptoms of nervous hyperactivity. The renal hemodynamic changes may be abolished by spinal anesthesia.

4. ***Early essential hypertensives:*** Those who already have established hypertension.

A discussion of the criteria for making these diagnoses will not be given, but I wish to point out that in my opinion this is one of the most important fields for clinical investigation in the whole domain of cardiovascular disease.

Neurogenic Hypertension: Symptoms and signs of a disordered nervous system in certain hypertensives long ago led to the belief that in many, at least, the disease was caused by increased activity of vasomotor nerves. But objective evidence was not obtained that this was so. Indeed, so extravagant and uncritical were some authors in their assumption of the correctness of this view that a reaction against it was initiated, culminating in the belief that the nervous system had nothing whatever to do with hypertension. The swing is now again in favor of its importance in the genesis of certain cases of hypertension.

It is well to remember that the term "neurogenic" signifies that the hypertension has its origin in the nervous system probably by increasing the number of impulses carried by the vasomotor nerves. Strict proof that hypertension is ever so caused is not at hand, but certain scanty evidence suggests that it might be true.

It is possible that the neurogenic element reaches its zenith in the early phase of hypertension to be supplanted later by the humoral mechanism. The suggestion has been entertained that it is just the other way around. There is no proof for either view.

An interesting example of the possibility of a neurogenic origin of hypertension has been described by Friedman and Kasanin.[21] They found hypertension in only one of two identical twins. It is generally assumed that the hereditary pattern of identical twins is alike and hence the presence of a disease in one and not in the other tends to minimize the importance of the hereditary component. Renal blood flow and glomerular filtration rates were similar in the hypertensive and normotensive twins, but the psychological patterns were very different. From these facts it was suggested that the psychological pattern was of primary etiological significance.

From bedside observation, two clinical pictures have been observed which strongly suggest the important participation of the nervous system in the genesis of the hypertension. The first of these, hypertension with manifestations of a neurosis, need not detain us. Suffice it to say that no sharp syndrome emerges nor, indeed, any clear idea as to how the neurosis brings on the hypertension, if it does. Some clinicians picture it as a suppressed chronic rage, perhaps akin to the sham rage of decerebrate animals. The second, the hypertensive diencephalic syndrome, presents a clearly defined clinical picture, but the evidence in favor of its being of neurogenic origin is only by analogy. Regardless of its mechanism, it is important to differentiate it clinically because of its different course and prognosis.

The Hypertensive Diencephalic Syndrome: This syndrome was described as occurring usually in young and middle-aged women, though it may be seen occasionally in men. It is characterized by hypertension of the labile sort, but especially by the periodic appearance of a blotchy blush which extends down over the face and upper chest, seldom, if ever, involving the limbs. Indeed, the latter are usually cold and have a dusky, mottled hue. Over the area of blush are minute beads of perspiration. Lachrymation or merely "watering" of the eyes may occur without an associated emotional counterpart. Tachycardia and hyperperistalsis are common. These episodes may occur without any apparent reason or may be brought on by embarrassment and excitement. The diagnosis of Graves' disease is often made because of these signs and symptoms and because the thyroid gland may exhibit slight diffuse enlargement and the basal metabolic rate may be elevated from +10 to +30. Subtotal thyroidectomy is of no benefit to these patients, yet it is the rare patient with this syndrome who escapes this operation.

The syndrome was called "diencephalic" because almost identical signs

can be brought on by diffuse stimulation of the diencephalon in human beings.

It is worth recognizing this syndrome, not only that an operation on the thyroid gland may be avoided, but also because the prognosis seems to be on the whole better than the more usual varieties of essential hypertension. Schroeder and Goldman have shown in susceptible persons the syndrome can be reproduced by intradermal injection of 0.25 mg. of histamine.

Pyelonephritis: The bedside picture of pyelonephritis often closely simulates that of essential hypertension, especially when the disease is well established, and for that reason, a constant search should be made for it. Unfortunately for the clinician, by no means all cases exhibit large numbers of pus cells in the urine, positive urine cultures and abnormalities in the pyelogram. There appear to be certain characteristic hemodynamic changes in the kidneys as determined by clearance measurements, but these need not detain us here. Often the history strongly suggests the correct diagnosis and if the characteristic urinary findings are present, it can be made with little difficulty. But if they are not, and this is not unusual, the more elaborate clearance studies may be necessary.

Unilateral pyelonephritis is not common.[2] When the diagnosis can be made with reasonable certainty, and if the hypertension which may be associated with it is no more than three to five years' standing, nephrectomy may reduce the blood pressure to near normal.[64] This is by no means an invariable phenomenon, since it depends on the state of the vessels, on whether the other kidney has become involved in the disease, etc.

Essential Hypertension: There may be no symptoms or signs accompanying this disease. The annual physical examinations, insurance examinations, and all such mass examinations of supposedly normal people, uncover large numbers of hypertensives, mostly of the essential variety. The patient is usually quite as surprised as the examiner to find the elevated blood pressure. On the other hand, many cases begin with dull morning headaches, increasing irritability, palpitation and pain over the precordium, insomnia, and a host of varied symptoms and signs, none of which is pathognomonic.

Physical examination reveals constriction of the retinal arterioles and often some sclerosis. If the disease is well established, and espe[illegible] f heart failure is not far off, arteriovenous nicking [illegible] heart may be noted as rapi[illegible] with the be quiet and unobtrusive [illegible] ...ly seen in the x-ray boot shape which the he[illegible] photograph. Both the sy[illegible] and diastolic pressures are elevated, the former proportionately greater than the latter, hence the wide pulse pressure.

Laboratory examination shows a number of interesting changes. The electrocardiogram confirms the finding of card[illegible] ophy and is used at times to ascertain its [illegible] in the diagnosis of the very [illegible] and thrombosis needs no cor[illegible] ...on two counts: first, if

the cardiac output is increased, the chances of the patient having essential hypertension alone had best be reexamined; second, the output of the heart supplies one part of the formula which measures peripheral resistance, an important datum in the clinical analysis of the state of the circulation.

No *single* clinical test of renal function is quite so useful as the maximal ability to concentrate urine. There are many ways to do the test, but in principle it depends on the interdiction of water for twenty-four hours with collection of the urine specimens in the last twelve. The specific gravity of this specimen is determined with care, and correction made for any increased amounts of protein in it and for temperature. The ability to concentrate urine is reduced very early in the course of hypertension; well before, for example, urea clearance.[11] The chief disadvantage of this measurement is that it is useless and misleading when the patient has evident or occult edema. A dry period when edema is present will cause a shift of water from the tissues to the blood, giving figures for concentrating ability much too low It should be noted, also, that late in the disease, this test is of no value.

The inulin clearance test which measures glomerular filtration and the Diodrast clearance test which measures tubular function and renal blood flow are of great usefulness in the study of hypertensives, particularly when combined with the determination of the so-called Tm_D or "tubular mass" The latter is a measure of the total functioning mass of tubular cells in the kidneys and it gives knowledge not gained by any other method, except roughly by tests of concentrating ability. Recently greater practicability has been achieved by the use of mannitol for filtration, p-aminohippurate for blood flow.

A useful calculation can be made by dividing the figure for inulin clearance by that for Diodrast clearance. This so-called *filtration fraction* represents the fraction of plasma water filtered and gives, therefore, a measure of intraglomerular pressure.

Diodrast clearance is usually low in established hypertensives, while, inulin clearance is maintained by the increased intraglomerular pressure. The increased intraglomerular pressure is due chiefly to constriction of the efferent glomerular arterioles and to rise in systemic pressure. Actually, from a mathematical analysis of the renal hemodynamics,[35] it appears that constriction of the afferent arteriole has occurred as well, and in some cases precedes efferent constriction. The increase in resistance of the afferent arteriole seems to protect the fragile glomerular capillaries from the increased systemic pressure, cancelling it out, so that the back pressure of the constricted efferent arteriole is probably the origin of the increased intraglomerular pressure. The special relationship of inulin to Diodrast clearance found in essential hypertension leads to a rise from the normal filtration fraction of 0.17 to 0.23 or above. If the plasma proteins are normal, the occurrence of an increased filtration fraction is presumptive evidence of essential hypertension.

It needs emphasizing that the initial state of the blood vessels and their response to the disease usually determine the prognosis in essential hypertension. Elevated blood pressure as such does not seem to be a highly

detrimental influence except insofar as it puts added strain on the blood vessels and heart. Intimal hyperplasia with narrowing of the vessels leads to a gradual choking off of the blood supply to the tissue with resulting progressive deterioration. It is the close study of the blood vessels which is so rewarding in hypertensive patients, for in these vessels is reflected a true measure of the severity of the disease.

The Malignant Syndrome or Malignant Hypertension: The malignant syndrome may appear during the course of several apparently dissimilar diseases all having the common denominator of hypertension. Some clinicians believe that it may be present practically from the onset of the hypertension, although certainly the great majority of patients who exhibit it have had preceding hypertension for several years I am one of those who believe that it may occur without preceding essential hypertension

The syndrome is characterized chiefly by two findings: (1) papilledema, hemorrhages, and exudates in the eyegrounds, (2) rapidly progressive course. Other changes in the eyegrounds are often seen, such as edema or detachment of the retina, marked changes in the blood vessels, arteriovenous nicking, etc. The blood pressure need not be exceptionally high nor the shift from essential hypertension to the malignant phase be marked by any significant change in arterial pressure. As the disease progresses, the pulse pressure tends to be reduced. The rate of increase in the size of the heart is often accelerated and heart failure is a common cause of death. The T waves in the electrocardiogram in Leads I and II are likely to become inverted early in the disease. The kidneys are also seriously injured and this is shown by the occurrence of hematuria and rapidly falling renal efficiency. Urea clearance, for example, may fall from 60 per cent of normal to 15 per cent in the course of several weeks.

The widespread necrotizing hemorrhagic arteriolitis and arteriosclerotic change which characterizes this syndrome are undoubtedly the causes of the rapid deterioration of the patient. The usual life span after its appearance is two to four years. It may be very much less or, on occasion, several years more. In a few patients the process seems to be rhythmic; the eyegrounds temporarily clear, only to be followed by another bout with the arteriolitis. It seems safe to say that malignant hypertensives seldom get well spontaneously.

B. PATHOGENESIS

Production of Experimental Renal Hypertension: The kidneys have been thought to be the cause of hypertension, since the time of Bright. Interest in them has waxed and waned as evidence for or against their participation appeared. It is perhaps not sufficiently realized that hypertension of renal origin was produced in animals as far back as 1905. Simple reduction in the amount of renal tissue produces it. Another method consists of occlusion of a part of the branches of the renal arteries. A third method consists in producing passive hyperemia of the kidneys by partial occlusion of the renal veins. In 1933 roentgen ray irradiation was shown to constitute a fourth method. There was, therefore, no doubt that suitable operations on the kidneys produced hypertension.

Loesch stated that hypertension could be produced by intermittent partial occlusion of the renal pedicle. A month or more was required for it to appear. The method was an interesting one but cumbersome. Goldblatt *et al.*[24] believe the hypertension in Loesch's experiments was due to persistent constriction of the renal vessels due to scarring. The argument concerning the participation of the kidneys in hypertension was finally clinched by Goldblatt, Lynch, Hanzal, and Summerville who demonstrated in classically simple fashion that application of a clamp to the renal artery caused persistent hypertension without renal excretory insufficiency. The latter finding was of especial importance. This method has been subsequently widely used and has done much to stimulate work in the field of hypertension.

A later method to be reported is that of Page in which the parenchyma of the kidney is held firmly by the fibrocollagenous hull[26] induced by Cellophane or certain types of cloth. It has been shown clearly that the vessels need not be included in the scar to produce the hypertension and that pressure on the parenchyma is enough.

Selye[65] has reported that compression of a renal artery sufficient to stop glomerular filtration, but still allowing enough blood for the tubules, causes loss of excretory function and replacement of the normal morphological pattern by aggregates of large cells which resemble those of the adrenal cortex. In this "endocrine kidney" seem to be dissociated the vascular and excretory functions with only the former persisting. Rats subjected to this procedure exhibit severe hypertension.

A few investigators believe that occlusion or partial occlusion of the ureters also produces hypertension. It may be true that it occurs in rats but it is extremely doubtful if it does in dogs or man.

Pathogenesis of Essential Hypertension: If the bulk of the more modern work on experimental hypertension is to be accepted as having possible application to essential and malignant hypertension in man, we must examine briefly the evidence indicating the similarity. Simple mechanical obstruction to the renal circulation in patients is common, and the important fact to bear in mind is that experimental work has demonstrated the importance of alteration in the renal circulation in the initiation of hypertension.

Alteration of the circulation by a fibrocollagenous hull around the parenchyma of the kidney is only occasionally observed in patients. Clinical examples are to be found in the Wilms' tumors, hulls resulting from trauma, hematomata, tumors, etc. But these are relatively rare.

The facility with which hypertension can be elicited in animals has accelerated work on the analysis of the mechanism of it and comparison with hypertension as observed in man. Table 2 shows the relationship of hypertension produced by alteration of the renal circulation, human essential hypertension and hypertension produced by angiotensin.[44]

It will be at once apparent that there is definite parallelism if allowance is made for the differences in anatomy and physiology of animals and man. For example, the relatively simple organization of the animal's nervous

TABLE 2

Comparison of Experimental Renal Hypertension, Human Essential Hypertension, and Hypertension Induced by Angiotensin

Experimental Renal Hypertension	*Human Essential Hypertension*	*Angiotensin Hypertension*
Heart		
Hypertrophy, left ventricular	Same	
Force—increased	Increased	Increased
Work efficiency—increased	Increased	Increased
Output—normal or reduced	Normal or reduced	Normal or reduced
Coronary sclerosis—not found	Common	Not known
Rate—normal	Normal	Normal or slowed
Pulmonary arterial pressure—normal	Normal	Increased in acute experiments
Venous pressure—normal	Normal	Often elevated in acute experiments
Kidneys		
Thickening of arteries—common	Common	Not known
Early morphological changes—none	None	Not known
Maximal ability to concentrate—reduced early	Reduced early	Not known
Glomerular filtration—maintained	Maintained	Maintained
Blood flow—normal or reduced	Normal or reduced	Reduced in acute experiments
Filtration Fraction—elevated	Elevated	Elevated
Diodrast Tm—slowly reduced	Slowly reduced	Slightly reduced
Renin secretion—increased	Increased	
Unilateral renal disease—sometimes cured by nephrectomy	Same	
Liver		
α_2 globulin production—possibly increased	Possibly increased	Not known
Eyegrounds		
Arteriolar constriction—present	Present	Present
Arteriolar sclerosis—present	Present	Not known
Hemorrhages—exudates present	Present	Not known
Papilledema—present	Present	Not known
Retinal detachment—present	Present.	Not known
Central Nervous System		
No evident change	Many somatic expressions of hyperactivity in some patients Need be none	None

Experimental Hypertension	Human Essential Hypertension	Angiotensin Hypertension
CENTRAL NERVOUS SYSTEM (Cont'd)		
Sympathectomy—no change in blood pressure	May reduce blood pressure	Does not affect response
Adrenalectomy—reduces arterial pressure	Probably reduces pressure	Reduces response only terminally
Hypophysectomy—reduces arterial pressure moderately	Possibly reduces pressure	No marked reduction in responsiveness
Thyroidectomy—no effect on pressure	No effect	.....
Pancreatectomy—no effect on pressure	Not known	No effect on responsiveness
Gonadectomy—no effect on pressure	No effect.	No effect on responsiveness

system, or the fact that animals do not walk erect, must make for marked differences in their response to hypertensive stimuli.

Despite the evidence in favor of the renal origin of essential hypertension, observations have been made which do not support this viewpoint.[48] One problem, however, merits consideration: whether arteriosclerosis precedes and initiates hypertension or whether it is a result of it. The controversy over this point was probably initiated by a finely executed investigation of Moritz and Oldt which strengthened earlier observations that organic arteriolar disease of the kidneys was almost always seen at autopsy of patients who had died from essential hypertension. It was concluded that this was evidence in favor of the renal pathogenesis of hypertension.

The logic in this reasoning seems odd. It is difficult to understand how the finding of arteriolar change in the kidneys, when the disease has run its course, tells anything about the factors initiating the disease. The only evident way to solve such a problem would be to study the renal vessels early in the disease, as Castleman and Smithwick[6] have done. They found, in contrast to the almost invariable occurrence of well-developed arteriolar disease in the kidneys of hypertensive patients observed postmortem, 28 per cent of the renal biopsies of 100 hypertensive patients (average age thirty-nine years, average blood pressure 210/130 mm. Hg) showed no, or insignificant, vascular disease. Even at necropsy the difference in caliber between sclerotic vessels of hypertensive and nonhypertensive patients was insignificant. Thus, Lisa, Eckstein, and Solomon[38] found only two examples among 100 necropsies in which there was the possibility that obstruction was sufficiently great to produce ischemia. Dock[13] has also stressed the evidence in favor of the view that renal arteriosclerosis may be a sequel and not a cause of hypertension.

Renal arteriosclerosis occurs in patients with diabetes in nearly half of those with systolic blood pressures below 140 mm. Hg, according to Bell;[8] yet, as the blood pressure in diabetics rises, the incidence of renal arteriosclerosis also rises. Thus, either hypertension or arteriosclerosis may exist without the other, but some vascular disease may intensify the hypertension.

Turning from the clinical evidence to the experimental, the experiments of Wilson and Byrom are enlightening. They were able to show that in rats partial occlusion of the renal artery of one kidney led to hypertension. Histological changes were often found in the intact, opposite kidney which were similar to those of malignant hypertension in man They concluded that these changes are due to the vascular strain imposed by the rapidly developing hypertension, renal failure apparently playing no part in their origin. Goldblatt had found much the same lesions in dogs but concluded that hypertension plus renal insufficiency are essential factors in their causation. Further work on rats by Friedman, Jarman, and Klemperer[19] showed that unilateral renal injury by means of the Cellophane perinephritis method led to hyalinized and necrotic vascular lesions associated with rapidly rising severe hypertension, but renal insufficiency was not a necessary factor for the development of arterial lesions.

Most evidence suggests, therefore, but does not prove, that hypertension may be initiated in the absence of renal arteriosclerosis as demonstrated by the usual methods of pathology.

It is possible, though there are no observations to substantiate this view, that some change in the properties of the vascular wall occurs not discernible in stained sections under the microscope which alters the intrarenal hemodynamics in such a way as to cause the liberation of renin. The terms "organic change" and "arteriosclerosis" may be misleading in that they indicate only gross changes visible under the microscope. This seems a very limited viewpoint and one that might well be discarded in the search for factors initiating hypertension.

Participation of the Kidneys in the Genesis of Hypertension in Man: Ever since 1938 there have appeared published reports of the finding of diseases, or anomalies, of the renal blood vessels associated with the onset and maintenance of hypertension. Howard *et al*[32] in 1954 gave great impetus to the better delineation of this problem by suggesting the wide use of aortography and split renal function tests for the diagnosis of renal vascular disease

In the Cleveland Clinic the important step has been taken of showing that surgical correction is followed in the majority of patients by significant remission or cure of the hypertension.[16,52] Poutasse has developed unusual skill in aortography so that the radiograms show the main renal vessels as well as those in the parenchyma with clarity. I am convinced that Poutasse's improvement in radiographic technic and interpretation has done much to put the diagnosis of renal vascular lesions on a firm basis.

By far the most common lesion found has been obstruction by atherosclerotic plaques. Then follow a large variety of lesions, such as thrombi, stenosis, thromboangiitis, and the like.

It is impossible at present to state the incidence of renal vascular lesions that are severe enough to be the cause of hypertension. Suffice it to say that we have found thirty patients with unilateral or bilateral obstructive lesions of the renal arteries in 104 selected hypertensive patients. It must be remembered that clinics such as ours, having some degree of specialization, draw a selected clientele.

Participation of the Nervous System in the Genesis of Hypertension: Until recently, most investigators and clinicians favored the view that a hyperactive nervous system showered the blood vessels with impulses causing constriction and elevation of arterial blood pressure. In animals with renal hypertension, it is possible to remove, portion by portion, a part of the nervous system and ascertain its effect on the arterial pressure. Renal denervation, supra- and infradiaphragmatic resection of the splanchnic nerves, anterior spinal nerve root resection from the sixth dorsal to the second lumbar segment inclusive, "total" sympathectomy combined with cardiac denervation, and, finally, destruction of the spinal cord—none of these procedures abolished the hypertension and only one, destruction of the cord, appreciably modified it. So, in dogs at least with renal hypertension, it is probably fair to assume that the nervous system is not the primary genetic agent mediating hypertension. But since the complex nervous system and the erect posture of man are not found in dogs, to mention but two differences, it is not safe to conclude that results obtained from studies on dogs' nervous systems are directly applicable to man. It is possible, however, that the difference between man and animals in their response to these operations is a quantitative and not a qualitative one.

It has long been known that the buffer nerves have a powerful regulatory action on arterial pressure and that, curiously, this mechanism seems to be working normally in the hypertensive, not as might be expected to reduce the blood pressure, but rather to maintain it at hypertensive levels. This paradox has now been explained by the demonstration of McCubbin, Green, and Page[12] that in dogs with renal hypertension the buffer mechanism is reset at higher levels if hypertension persists. During the very early phase of hypertension the carotid sinuses inhibit the vasoconstrictor centers in the medulla to reduce vasoconstriction and lower blood pressure. With time, however, the barostat becomes reset now at a higher level, and then attempts to lower pressure are resisted by volleys of impulses to augment vasoconstriction and heart rate. So this important regulatory system comes finally to work against the best interest of the patient.

The Endocrine System: Morbid changes in various of the endocrine glands beyond doubt can produce hypertension. Adrenal carcinomata or adrenal pheochromocytomata are excellent examples. Quite aside from the rare examples of endocrine hypertension, these glands appear to participate importantly in both experimental and essential hypertension. But, unfortunately, methods are not yet available for putting such clinical impression into more quantitative terms. In observing hypertensive patients, one is often struck by the odd assortment of signs associated with endocrine dysfunction. Hypertension, for example, is often associated with mild acromegaly or with diffuse enlargement of the thyroid gland. This is not

to suggest that these conditions are the cause of the disorder but merely that clinical characteristics which we have accustomed ourselves to associate with endocrine disorder show themselves with varying degrees of subtlety in many patients with hypertension.

There is experimental evidence to substantiate these clinical impressions. Let us start with the "master gland," the pituitary. Its removal in normal and hypertensive animals is associated with a moderate prolonged fall in arterial pressure when the somatic changes which characteristically occur after hypophysectomy or diencephalic injury are observed. Conversely, the rise in arterial pressure is *usually* not as severe or prolonged when hypertension is induced. The effect on blood pressure is only minor, but none the less significant. Activity of the hypophysis in normal animals tends to accentuate blood pressure changes; hence, in its absence they are slightly damped. No evidence is as yet available as to how much diencephalic injury participates in these effects of hypophysectomy, for the diencephalon is almost always slightly injured by the operation itself, quite aside from any loss of connecting nerve fibers with the gland. Certain it is that the pituitary gland is not primarily responsible for the hypertension.[23]

The adrenal glands have a more profound effect on arterial pressure. Their removal in hypertensive dogs is accompanied by a sharp fall and, unless treatment with cortical hormone is begun, the blood pressure may remain subnormal. Intensive treatment causes moderate elevation in pressure but not usually to the original hypertensive level. These results of adrenalectomy seem to be due to loss of cortical rather than medullary tissue. The way in which the adrenal glands participate in the mechanism of hypertension is not known.

Skelton[81] has described an interesting form of hypertension which occurs in uninephrectomized, young, female, salt-treated rats during regeneration of the adrenal cortex. Because of the similarity of this condition with that resulting from overdosage with adrenal steroids, it was postulated that some functional abnormality of the regenerating adrenal cortex was concerned. No evidence for this has yet appeared. It would usually be assumed that a regenerating gland would be a hypofunctioning one, which makes Skelton's observation more surprising.

Study of the body's nonspecific responses to damaging agents led Selye to adapt the older concept of George Crile and others to a more modern setting. Initially known as the "alarm reaction" and later changed to the "general adaptation syndrome," these views have proved a potent stimulus to experimental work. Under conditions of repeated stress, the secretions of the adrenal glands are supposed to be so great in amount and perverted in character as to elicit widespread arterial damage, and, probably by renal vascular damage, the onset of renal hypertension. In rats, for example, hypertension and extreme vascular change are induced by removal of one kidney, administration of high salt or protein diets and massive doses of desoxycorticosterone acetate. In normal dogs and man, the effects are less certain, some investigators finding a rise in pressure, others not. But in patients with Addison's disease, there is no doubt that DOCA elevates

blood pressure and causes cardiac hypertrophy. Some investigators find that intravenous injection of DOCA dissolved in propylene glycol elevates pressure in human beings while others find only a slight effect but due to the propylene glycol. Selye's evidence suggests that stimulation of the adrenal glands originates in the hypophysis and that stimulation of the latter comes from the nervous system subjected to stress.

The general adaptation syndrome has not as yet been investigated in patients with essential hypertension, but it is hard to suppose that some parts of it will not be applicable to the complex mechanisms of the disease.

Hypertension may be produced by disturbances in either the medulla or the cortex. The pheochromocytoma, a chromaffin tumor of the medulla, causes first a paroxysmal type of hypertension which later may become sustained. In the later stage, the condition is difficult to distinguish from essential hypertension. Hypertension due to cortical disease is exemplified by adrenal carcinoma. Usually this neoplasm is accompanied by well-developed Cushing's syndrome, which can be distinguished from Cushing's syndrome of pituitary origin by the fact that, in adrenal carcinoma, excretion of male sex hormone is greatly increased.

Recently there have been described a number of patients having aldosterone-producing tumors of the adrenal glands in whom hypertension occurred.[29] The syndrome is characterized by episodes of muscular weakness, hypertension, polydipsia, imbalance of serum electrolytes, and low renal-concentrating power with excessive amounts of aldosterone in the urine. Hypokalemia, alkalosis and slight hypernatremia are usual. Electrocardiographic changes of hypokalemia may be the first clue to the correct diagnosis Aldosteronism should be suspected in patients with hypertension of unknown origin who, in the presence of adequate excretory renal function, excrete urine which is persistently alkaline, and who show also disproportionate loss of urinary concentrating power.[15] Removal of the adrenocortical tumor abolishes the signs and symptoms, and aldosterone disappears from the urine. Hypertension may or may not disappear. Usually it does.

The thyroid gland is the only other ductless gland commonly associated with hypertension. But the hypertension is of an especial sort, namely, moderately elevated systolic with slight or no rise in the diastolic pressure. It is due chiefly to increase in cardiac output which in turn seems to be a result of the increased metabolism of hyperthyroidism.

The ovaries have commonly been considered as important organs in the genesis of hypertension. The term "menopausal hypertension" has been in use many years, and physicians have believed that the menopause unleashes hypertension which was perhaps latent. A clinic in the Indianapolis City Hospital was set up to determine whether hypertension was commoner than usual in a large group of castrated women. These women were of widely different ages. It has now become clear that after surgical removal of the ovaries, hypertension is no more common than in noncastrated women of the same age group. In short, we do not believe that hypertension in human beings is due to loss of ovarian secretion.

TABLE 3

DIFFERENTIAL DIAGNOSIS OF THE HYPERTENSIVE DIENCEPHALIC SYNDROME, HYPERTHYROIDISM, AND PHEOCHROMOCYTOMA

	Diencephalic Syndrome	*Hyperthyroidism*	*Pheochromocytoma*
Preponderant Sex	F	F	Equal
Age	Young Adults	Young Adults	Uncertain
Arterial Pressure	Systolic and Diastolic Hypertension	Systolic Hypertension	Paroxysmal or Sustained Hypertension
Response to Iodine	0	+	0
Response to Subtotal Thyroidectomy	0	+	0
Cardiac Hypertrophy	+ +	+	+ +
Eyegrounds	Arteriolar Constriction	0	Arteriolar Constriction may be transient
Cardiac Output	Normal	Increased	Normal except during paroxysms of hypertension
Skin	Blotchy Blush	Unusually Warm	Pale or Red
Perspiration	+ +	+	+ + + + During Paroxysm
Basal Metabolism	+	+ + + +	+
Appetite	Often Poor	Excessive	Often Poor
Rise in B.P. Following Massage of Adrenal Area	0	0	+ + + +
Urogram	0	0	Often shows renal displacement by tumor
Thyroid Gland Enlargement	+	+ + +	+
Tachycardia	+ +	+ + + +	0
Exophthalmos	0	+ + +	0
Mental Status	Neurotic	Hyperactive	Normal
Weight Loss	0	+ + + +	+
Prognosis	Fair	Good	Fair
Tremor	Coarse	Fine and Coarse	0
Tightness of Scalp Felt	+ + +	0	0

Clinical Differentiation of "Neurogenic" and Endocrine Hypertension: We have discussed briefly certain observations which suggest, but by no means prove, that "neurogenic" and possibly even "endocrinogenic" factors actually participate in the genesis of essential hypertension. The extreme examples of these, *i. e.*, the diencephalic syndrome for the "neurogenic" and pheochromocytomata for the "endrocinogenic" have been described to emphasize the pattern of each in order that the less obvious but similar patterns be recognized in patients with the more usual forms of essential hypertension.

Table 3 gives the clinical differentiation of the "neurogenic" hypertensive diencephalic syndrome, and the "endocrinogenic" hyperthyroidism and adrenal pheochromocytoma. It is worth consideration because many of these signs or symptoms occur to a more or less marked degree in essential hypertensives and their combination is often confusing. If one has some knowledge of their mechanism and possible origin it seems to me to aid in the analysis of the varied types of hypertension.

It must be evident that examination of hypertensive patients to ascertain to what extent the various systems—glandular, nervous, and renal vasopressor—are contributing to the cause of the hypertension and, contrariwise, how the body is withstanding it, is still in a far too nebulous stage. In short, a blood pressure measurement and urinalysis are no longer an adequate examination for a patient with hypertension.

Humoral Mechanism of Hypertension: Most evidence suggests that the mechanism causing established hypertension is a humoral or "chemical" one, and many pressor substances have been thought to be the especial substance causing the hypertension. For example, epinephrine from the adrenal glands or "urohypertensin" from the urine have long been suggested as possibilities. But there are certain physiological properties that the true effector of hypertension must possess which most pressor substances do not have These properties will be described subsequent to consideration of a substance which seems to possess most of them.

In 1898 Tigerstedt and Bergmann showed that crude extracts of kidneys cause a rise in arterial pressure when injected into rabbits. This work received only desultory attention until it became clearer that the kidneys could actually initiate hypertension. The active substance contained in these crude extracts was called *renin*, which was believed to be a pressor substance in itself. But when it was purified and assayed both in the dog's tail perfused with Ringer's solution and the intact cat, it was found by Kohlstaedt, Helmer, and Page that the more it raised arterial pressure in cats the less vasoconstrictive it became in the perfused dog's tail. This experiment demonstrated that renin itself was inactive as a vasoconstrictor in the absence of some other substance. This other substance was found to be a protein contained in plasma.

Renin: Renin is an enzyme contained in the tubular cells[20] of the kidneys and is not in itself a pressor substance. It has not been crystallized but has been partially purified. It is species specific. It may be defined in quantitative units by measuring its enzymatic activity.[67]

Renin Substrate (α_2 Globulin) (Renin-Activator, Hypertensinogen): The protein substrate on which renin acts was found by Page and Helmer[53] and subsequently shown to have the same electrical mobility as α_2 globulin.[54] It has its origin in the liver.[37,65] Study of the reaction between renin and substrate has clearly established the fact that it is enzymatic.[56] This explains the observation that when renin is injected into animals, the rise in blood pressure is slow and exceptionally prolonged Some time is required for the reaction to occur and angiotensin to be liberated.

The amount of renin-substrate in the blood seems small because injection of renin soon exhausts it and this accounts *in part* for the phenomenon of tachyphylaxis, *i. e.*, refractoriness which develops as the result of repeated injections of renin (Fig. 1).



FIGURE 1 The rise in the arterial pressure resulting from repeated injections of renin. It will be noted that the response is less after each injection.

A good deal of discussion in the literature has arisen over the terminology employed for renin-substrate.[54] When it was first discovered, it was called "renin-activator" for the simple reason that in its absence renin was inactive. Later, when the reaction product had been identified as angiotonin by Page and Helmer and hypertensin by Braun-Menendez, Fasciolo, Leloir, and Muñoz, the South American group proposed the use of the term "hypertensinogen" for the substrate. However, terms such as "hypertensin," selected to imply a causal relationship to hypertension in the absence of proof that this is so, seem undesirable. Further, the suffix "ogen," in the term "hypertensinogen," usually refers to a substance, which, by molecular rearrangement, gives rise to another substance, often itself an enzyme, *e. g.*, pepsinogen, trypsinogen, etc.

The purely descriptive word "renin-substrate," therefore, seems the simplest and most accurate connotation with the postscript α_2 globulin when it is considered useful to indicate its presence in the protein fraction α_2 globulin.[28]

Angiotensin (Angiotonin or Hypertensin): The product of this reaction was formerly called "angiotonin" or "hypertensin," but now, by common consent the term, "angiotensin" is employed. The first product of the reaction of renin on renin-substrate is a peptide containing ten amino acids. The decapeptide has some pharmacological action. The blood, however, contains an enzyme which splits off two more amino acids to form an eight-membered peptide or octapeptide. This substance is the most active pressor agent known.

Angiotensin was synthesized in 1957 by Bumpus, Schwarz, and Page[5] and by Rittel *et al.*, and is now widely available for investigation.

When injected or infused into animals or man, angiotensin reproduces most of the hemodynamic changes associated with essential hypertension itself. Because of this and the circumstances surrounding its formation, it is generally believed to be far the most likely humoral agent concerned in the mechanism of renal, and perhaps of essential, hypertension.

So far, attempts to measure the concentration of this agent in blood have not been notably successful. The methods currently available have not been proved quantitative and probably are not nearly sensitive enough. When a suitable quantitative method is found, it should provide a ready method for the diagnosis at least of renal hypertension.

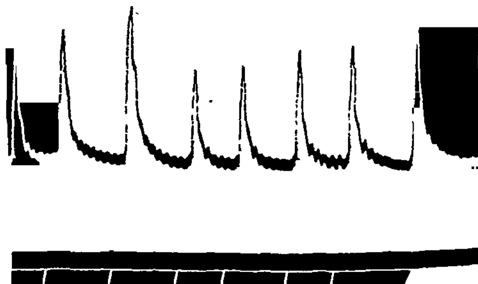
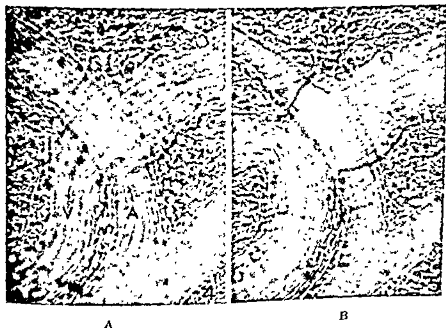


FIGURE 2. The pressor effect of angiotensin when injected into a cat with its central nervous system destroyed. It will be observed that there is little latent period before the rise in arterial pressure begins

Is Angiotensin the Chemical Mediator of Hypertension? (a) Liberation from the Kidneys: It has been often stated that "ischemia" of kidneys was the initiating factor in the production of hypertension, but data have not been presented to prove this. On the contrary, most evidence shows[10] that hypertension can be produced without measurable ischemia. Furthermore, since some patients with essential hypertension have no renal ischemia, if the human disease is simulated in the experimental, then ischemia must not be a *necessary* condition for the production of experimental hypertension.

It is by no means certain just what vascular or other change initiates the liberation of renin with the consequent formation of angiotensin. Lowering the blood pressure as the result, for example, of hemorrhage or shock seems to be one condition under which it occurs.[illegible] Reduction of intrarenal pulse pressure seems to be another and perhaps much more common.[34] Indeed, it may be the factor which liberates it in renal hypertension.



A B

FIGURE 3, A. Photomicrograph showing the normal appearance of a branching arteriole and a venule in the bay of a moat chamber, twenty-six minutes before the intravenous injections of 1.0 cc of angiotensin The arrows indicate the direction of blood flow. *A*, arteriole, *V*, venule

FIGURE 3, B Photomicrograph of the same vessels shown in 3 A, 1 0 minute following the injection of 1.0 cc of angiotensin This was the time of maximal arteriolar constriction produced by the angiotensin As shown in this photomicrograph, the arteriolar wall became thicker during constriction The flow of blood was not interrupted.

(Abell, R. G, and Page, I H · J Exper Med. 75·305, 1942)

Thus, neither chronic renal ischemia nor reduction of renal arterial pressure can be the initiating factor in experimental renal hypertension, and indirect evidence from renin liberation by isolated kidneys suggests that the immediate mechanism is reduction of intrarenal pulsation. Such is in fact the only common hemodynamic change in the two major forms of experimental renal hypertension. A metal clamp on the renal artery can damp the pulse before it reaches the kidney and a rigid hull of scar can hold the organ indistensibly in its grasp, pulsation becoming impossible. The ... and exudative proliferation which characterize

they enclose as does the experimental perinephric hull to the kidney it enfolds.

Whatever the circumstance which sets the renal vasopressor system in motion, renin is liberated, acts on the renin-substrate and angiotensin is liberated, presumably near the site where it must act, *i. e.*, the arterioles.

(*b*) *Action on the Arterioles*· Observation of patients with hypertension must convince the physician that blood flow through the peripheral tissues is entirely adequate. This means that if the arterioles are constricted the effects of the constriction are balanced by either an increase in the force of the heartbeat or output of the heart or both.

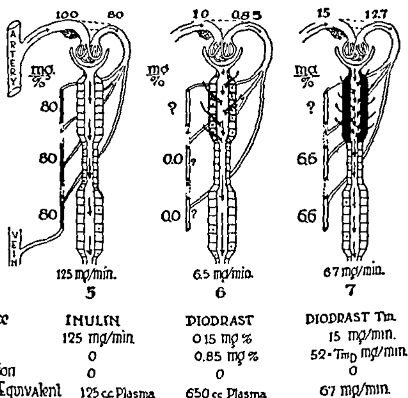


FIGURE 4 Schematization of inulin and Diodrast excretion The schematized nephron in each case represents the normal function of an adult human being. The numerals in mg per cent refer to the concentration of inulin and Diodrast in the plasma, the values noted as mg./min. to the concurrent rate of excretion. Direction of arrows indicates paths of transfer of the substances, and shading of tubules, the extent of their participation in the transfer from blood to urine. (Corcoran and Page)

This special type of vasoconstriction is associated with rise in blood pressure of patients with essential hypertension. Vasoconstriction often occurs in local areas without rise in arterial pressure, as, for example, in Raynaud's phenomenon. It may be more widespread, also, as in shock or burns, yet blood pressure be low rather than high.[47] So vasoconstriction alone is not enough to raise blood pressure.

To achieve the nice adjustment found in hypertensives, it is necessary for the arterioles to constrict just enough and the force of the heartbeat to augment sufficiently so that pressure rises but perfusion of the peripheral tissues does not change. There are few pressor substances known which have anything like the properties required to reproduce this fine vascular adjustment. Angiotensin is almost unique in that it is able to do so.[1] This can be well seen in the vessels which grow into transparent chambers (Clark principle) placed in rabbits' ears. This method allows observation of the undisturbed vessels under the microscope. When angiotensin is injected into a systemic vein of rabbits, the arterioles in the ear and mesentery as well are seen to constrict, but despite arteriolar constriction, perfusion of the capillaries remains unchanged.[1]

(c) *Action on the Heart:* It should be a matter of no surprise that substances which cause marked vasoconstriction also can act on the heart itself for the heart is only a specialized portion of the vascular tree. Studies of the action of angiotensin on isolated perfused hearts show that coronary flow is decreased[30,39] while work performance and efficiency are increased[39] without change in heart rate. The results of studies on normotensive human beings differ somewhat from those on isolated hearts.[4,78] Intravenous injection causes rise in venous pressure, decrease in vital capacity and in stroke volume. Since the rate of the heartbeat is reduced only slightly or not at all, cardiac output falls. It should be observed that these properties of angiotensin are unlike all known pressor agents so far adequately studied.

The studies on isolated hearts fit well with what would be expected of a substance causing hypertension. Those in normotensive human beings are more difficult to interpret. The rise in venous pressure and decrease in vital capacity suggest heart failure,[78] but there are no other of the necessary conditions to substantiate the occurrence of this morbid state. It has been suggested that the "failure" might be due to coronary artery constriction and to lack of adaptation to the strain of the acutely increased blood pressure, a strain more efficiently countered in chronic hypertension.

The output c
normal or decr
tension as well.
decrease it, the
decreases. Angiotensin, however, decreases stroke volume without reducing the rate greatly, simulating the state of the heart in many hypertensive patients.

It seems reasonable to believe, then, that *so far as contemporary knowledge goes*, the action of angiotensin on the heart is what might be expected of the effector substance of hypertension itself.

(d) *Action on the Kidneys:* The action of angiotensin on the kidneys has been studied chiefly by clearance methods or by means of the thermostromuhr. Briefly, inulin and mannitol are excreted only by glomerular filtration. Their clearance (volume of plasma equivalent to the amount of inulin which appears in the urine each minute) is, therefore, equal to

the volume of glomerular filtrate formed each minute. On the contrary, Diodrast and p-aminohippurate are excreted largely by the tubules. Their removal from the blood is almost complete at low concentrations; hence, Diodrast and p-aminohippurate clearance are nearly equivalent to renal plasma flow, *i. e.*, the rate of flow to functioning tubular areas.

With these observations in mind, let us see what is to be expected from the kidneys when angiotensin is injected and how closely the result reproduces the intrarenal hemodynamic picture of hypertension itself.

In hypertensives, as was stated before, Diodrast clearance is usually reduced below normal levels while inulin clearance is maintained. This normal level of inulin clearance depends upon an increase in intraglomerular pressure. Decreased plasma flow, along with maintenance of filtration rate, must mean that distal to the glomerulus, an obstruction has been interposed to the flow of blood. This obstruction or valve is the efferent glomerular arteriole. Constriction of this vessel alone could lead to the changes in blood flow noted in the kidneys of hypertensives.

The picture is, however, not quite so simple as this. There is reason to believe that some obstruction to flow is interposed by the afferent glomerular arteriole as well. This would tend to reduce intraglomerular pressure. But since the systemic arterial pressure is high, any reduction in the size of the afferent vessels tends to be minimized.

Injection of angiotensin increases arterial pressure and decreases renal blood flow.[7] The rate of glomerular filtration is only slightly if at all decreased, because, as in hypertensives, there occurs increased extraction of water from the glomerular plasma (increased filtration fraction). Angiotensin, therefore, constricts the efferent glomerular arterioles, and it has been shown by calculation that the afferent arterioles may be constricted as well.[36] Thus, the hemodynamic picture in the kidney of hypertensives has been faithfully reproduced by the infusion of angiotensin.

The finding of normal blood flow in the kidneys of *some* early hypertensives has led to doubt that a pressor substance such as angiotensin could be concerned in the genesis of hypertension. Reflection will show, however, that on the basis of contemporary evidence this doubt is not well sustained. In general, the amount of blood which flows through the kidneys will be the resultant of two forces: (*a*) The systemic arterial pressure forcing blood through the kidneys; and (*b*) the resistance within the kidneys opposing the flow of blood.[10] If the rise in systemic pressure should increase out of proportion to the renal resistance, relatively more blood would flow through the kidneys. The finding of a normal blood flow under these circumstances would not mean that no vasoconstriction in the kidneys had occurred. On the contrary, marked and widespread constriction might be present, but its effect on blood flow minimized by the increased systemic pressure.

(*e*) *Symptoms and Signs:* Clinical observation has shown that hypertension, even of severe grades, may occur without symptoms or signs. Hence, a humoral agent believed to be a cause of hypertension must not produce them when a rise of arterial pressure occurs after its injection. Tyramine, Adrenalin, methyl guanidine, and Pitressin produce a wide

variety of symptoms, such as headaches, nausea, vomiting, bradycardia, palpitation, and peripheral blanching, in more or less severe form. Angiotensin, on the contrary, usually causes hypertension without symptoms or signs, at most slight breathlessness or throbbing in the head in a few subjects.

Thus, observations on the nature of the action of angiotensin are largely consistent with the view that it is the substance causing elevation of blood pressure in patients with essential hypertension or animals with experimental renal hypertension. But it should be recognized that only a beginning has been made in the study of the complex renal vasopressor system of which angiotensin is an important part. There is as yet no proof that essential hypertension is of primary renal origin; that there is at least important renal participation seems more than probable.

C. TREATMENT OF HYPERTENSION

1. General Measures: In a short space it is not possible to describe in detail the general measures so important in the treatment of hypertensive patients. This has been done in a manual for the patients themselves.[45]

Perhaps the principles of these general measures can be summed up as follows: (1) Cultivating serenity; (2) coming to terms with the inevitable; (3) living a life of moderation; (4) participating only in those affairs which one can influence; (5) avoiding fatigue; (6) having more frequent periods of rest; (7) avoiding obesity; (8) avoiding food fads and eating a well-balanced diet more frequently than usual; and (9) selecting a physician in whom the patient can place full responsibility for wise counsel. Each of these measures requires much thought and planning, and when carried out thoroughly and systematically will add much to the comfort of life and probably conserve life itself. Administered in a cursory fashion, both patient and physician lose invaluable aids.

Excessive nervousness contributes greatly towards keeping the blood pressure elevated. Its control is often a complex problem. If, as often happens, it is associated with the menopause, administration of 0.5 mg. of stilbestrol daily with meals may do much to relieve it. Occasionally, it is due to masked hyperthyroidism; when hyperthyroidism is the cause, treatment is [illegible] by the usual means. Phenobbital 0.03 Gm [illegible] continued for [illegible] tory when used under the physician's direction for insuring adequate sleep. Other more elaborate physical methods such as "progressive relaxation" will not be discussed in this short review. Psychoanalysis or psychiatric guidance has its place in the treatment of a few patients.

If hypertension occurs in association with one of those rare diseases such as tumor of the adrenal gland, clearly the treatment consists in removing the exciting cause. Less than 3 per cent of all patients will come under this category:

2. Nephrectomy: If it can be shown that disease is limited to only one kidney, removal of the diseased kidney has often been observed to be followed by return of blood pressure to normal limits. The difficulty has

been to determine whether disease is really limited. I have already given the indications for a penetrating urologic analysis of this problem.

Nephrectomy is usually done when anomaly or disease of the renal vasculature is surgically uncorrectable or when the parenchyma of the kidney is so badly damaged that segmental resection or other forms of repair would be of little avail. There is an attempt on the part of some of the better surgeons to preserve as much functioning kidney as possible by whatever method indicated.

It should be recalled that there is no direct relationship between excretory efficiency and the height of the blood pressure. Nor does the pyelogram give a clear idea as to whether hypertension may be expected.[86] Further, the time the hypertension has existed has not proved an infallible index of whether reversibility may be expected.[7] All this led to a wave of nihilism[25] which for a decade effectively discouraged nephrectomy as a treatment for hypertension. With the more discerning use of the arteriogram, pyelogram, etc., a much more rational approach is now being taken and the better results leave little doubt concerning the validity of nephrectomy in the treatment of selected hypertensive subjects.

3. Potassium Thiocyanate: This salt has had a checkered career in the treatment of hypertension. It was introduced many years ago but fell into disrepute because of toxic manifestations occasionally observed. It often is a most valuable remedy for intractable headaches that afflict hypertensives, especially when given once intravenously in doses of 1.0 gram. These appear to be its special virtues.

4. Extensive Sympathectomy: Dorsolumbar and splanchnic nerve resection as methods of treating patients with hypertension, just as thiocyanate, has been greeted with cheers or jeers. It is probably true that reasons initially offered for the performance of these operations were incorrect. And as a result, a flood of criticism greeted the work. Time has shown much of this has been unjustified. The field was further confused by those who attempted to transfer to human beings results obtained on animals with experimental hypertension, concluding that since in dogs these operations produced little or no reduction in arterial pressure, the same was true in man.

Probably, fortunately, sympathectomy for the treatment of hypertension developed empirically and before hypotheses were advanced to explain it. In fact, if it had depended on some of them it might never have been practiced. Thus, it has been suggested that the effect of the operation does not depend on denervation of the vasomotor apparatus of the abdomen other than the kidneys but rather on the relief of renal ischemia. In this view, renal denervation alone should be fully effective, whereas it has no effect. Further, the view depends on renal ischemia as the efficient cause of hypertension, whereas such ischemia is not uniformly present either in experimental hypertension or in hypertension in human beings. Lastly, the operation only rarely increases renal blood flow, which is usually unchanged after an otherwise satisfactory operation. The fact that renal blood flow does not usually decrease after sympathectomy when arterial pressure has fallen indicates that renal resistance must have

diminished and, although without reference to the hypothesis of renal ischemia, it has also been suggested that this fact establishes a beneficial and specific effect of renal denervation. This point of view too is defective in that it ignores the normal anatomy of the renal circulation by which the kidney varies its resistance with arterial pressure in order to maintain as well as can be a normal rate of blood flow. There is no reason to suppose that this mechanism is in any way defective in hypertensives. Indeed, there is good evidence from the renal hemodynamic effects of high spinal anesthesia to establish its presence and normal activity. The persistence of this intrinsic renal mechanism of regulation of blood flow after operation can scarcely be attributed to denervation. Sympathectomy only leaves the kidney where it was before and its effectiveness in lowering arterial pressure is therefore extrarenal.

There is now no doubt that when these operations are sufficiently extensive, as in the technic of Smithwick and the modified Adson procedure, a marked fall in both systolic and diastolic pressure occurs in many patients. This is most pronounced when the patient stands erect. Indeed, postural hypotension is one of the best indices of the completeness of the operation. The length of time blood pressure remains reduced is variable. The average is perhaps from three to five years, some less and others more.

It is not unusual for regression of the morbid changes in the eyegrounds of patients with malignant hypertension to occur. And one of the most striking changes is the loss of headaches and the regaining of a sense of well-being.

One of the greatest difficulties in the application of the method has been the inability to find any single or even multiple tests which will determine whether a favorable outcome is to be expected. The hypotensive effect of administration of Sodium Amytal has been most extensively used to ascertain the drop in pressure to be anticipated as the result of operation. Allen believes that when an adequate fall in pressure does not occur, the likelihood of success is poor, but that an adequate fall is no guarantee of success. Various authors have their own criteria and it now seems to be a matter of personal experience as to how patients are selected.

As we said before, the precise mechanism of the action of these operations is not clear. It is not improbable that several factors play a part, among these being a reduction of venous return to the heart as a result of denervation of extensive vascular areas. Besides this, the denervation of the large splanchnic area prevents the normal reactive vasconstriction from occurring when the patient moves from a horizontal to an erect posture.[9] Fainting is often observed presumably because this protective mechanism has been blocked in its action.

Thus it may well be that the overall reduction of blood pressure during any twenty-four-hour period may be quite significant and the time taken away from the destructive and sclerosing effects of the elevated pressure on the blood vessels contributed towards increasing longevity.

5. Kidney Extracts: The reasons for the search for substances in the kidneys which might lower blood pressure need not concern us here.

Although suitable extracts of kidneys have been prepared which lower blood pressure and cause improvement in the clinical condition of patients, the mechanism by which these extracts act is entirely unknown.

The term "nonspecific" has been employed to describe their action.[62] This may be true in the superficial sense of the word, *i. e.*, the lowering of pressure is due to an unknown mechanism set into action by a heterogeneous group of substances. Among these is fever, but many patients have fever without reduction in arterial pressure and *vice versa*. The important point to recognize is that if any form of therapy will lower pressure and benefit the patient it does not make a great deal of difference what the mechanism is.

It is the belief of a very few investigators that certain types of extracts of kidneys have these beneficial effects, but no one to date has been able to prepare an altogether suitable extract. Such a search is naturally a tedious and expensive job, since, in the last analysis, patients must be the test objects and nothing is known of the chemical nature of the substance sought.

There is some evidence which suggests but does not prove some degree of specificity. Kidney extract will reverse the intrarenal hemodynamic change usual in most cases of hypertension to a more normal one.[8] Further, cardiac output will be elevated in hypertensive patients when the mean pressure falls.[71]

It is quite clear that work along this line is still in its embryonic stage. None can foresee its outcome, hence the desirability of not attempting to codify knowledge in this field prematurely. Currently these extracts cannot be considered as therapeutic agents. They are interesting experimental tools.

6. Excessively Low Sodium Diets: The use of low sodium diets has been revived, but now the restriction is even more severe, often not more than 200 mg. of sodium being allowed in one day's diet. This level is extremely difficult to attain in most patients and is altogether impractical for some.

The results in our patients have been somewhat encouraging. At least 30 per cent show significant fall in arterial pressure and some feel better. Administration of salt to these patients is associated with a rise in blood pressure. It appears that there is a close association between the change in salt content of the diet and the height of the arterial pressure in these particular patients.

Occasionally, circulatory collapse occurs from the severe salt deprivation, hence the treatment has potential dangers. These can be exaggerated because most patients, when not in the hospital under rigorous supervision, do not keep their salt intake below 0.5 Gm.

Those of us who remember the era when low salt diets were being indiscriminately prescribed for hypertension recall that at times some lowering of pressure occurred apparently as a consequence of the low salt intake, but the intake almost never went below 1 Gm. of sodium chloride. It thus remains to be determined whether the drastic restriction

now suggested is really necessary. At best, not all patients will be benefited, but for these, it may well be worth the effort.[27,72]

The use of amberlite resins has been suggested as a shortcut to a salt poor diet.[14] Oral administration of certain types of these exchange resins seems to remove enough sodium from the intestinal contents to achieve the desired reduction. The use of amberlite resins in general practice is fraught with so many difficulties, it is very doubtful that these substances can be recommended. We do not use them. Potentially, they may do serious damage by removing other important constituents from the gastro-intestinal tract.

7. Rice Diets: There are few suggestions for the treatment of hypertension that have stirred so much controversy as the rice diet. Every shade of opinion currently exists. Some see in it a cure, while others view it as deserving of nothing more than casual interest. These views are colorful, even if not based on much substantial evidence. Many of us remember the extremes of view expressed 25 years ago about sympathectomy. This emotional approach, as one looks back upon it, contributed little to understanding of the nature of the problem.

The rice diet and the sodium depletion diet are alike in that each yields about 2000 calories fuel value and contains less than 0.5 Gm. of sodium. They differ in their protein content, which in Kempner's regime is less than 20 Gm., and in Kempner's assumption that other foods contain unidentified toxic substances, not present in rice, which embarrass the kidneys.

Are the effects of the diet due to its low salt content, to its low vegetable protein content, to loss of weight, or to a combination of these plus aggressive mass psychotherapy? There is now rather general agreement that the chief effect of the rice diet is in reducing the sodium intake. It is a simple and highly monotonous low-salt diet.

Our own experience with the rice diet has been extensive Some of our patients would not stay on the diet because of its monotony. Among those who did so after a prolonged control period, effects on the blood pressure have not been nearly so impressive as when the diet was started shortly after coming under our care. A fall in renal blood flow in some has occurred which has been reversible.

The divergent conclusions reached by different investigators lead only to the conclusions that one of the essential safeguards least employed is an adequate control period, and this in the face of the common experience that the level of arterial pressure may drop by 50 mm. Hg or more during the first few weeks of patient-physician contact. Casual blood pressure readings over even many years, however constant they may be, do not replace as controls frequent measurements before and during the periods of dietary control Another factor in prescribing the diet is the patient's enthusiasm for it. Very often he can only be persuaded to it by promises of relief or threats of serious complications which few physicians can conscientiously subscribe to Still, some encouragement may be necessary, for it is only the rare patient who will take a detached and scientific view of a rigid dietary scheme.

The effects of weight loss due to the diet have not been adequately evaluated. European experience during World War II would suggest that these play a much more important part in determining the decrease in arterial pressure than deprivation of animal protein and provision of protein of vegetable origin

Finally, in the presentation of data, it should be remembered that essential hypertension is a disease with an extraordinarily variable course, so that composite curves carry little meaning or conviction. Rather, the aim should be to present well-documented studies of individual cases, in which the factors of sodium loss, weight loss, hypometabolism, fluid shift, and, above all, the variability of arterial pressure under control conditions are presented in detail.

8. Chlorothiazide (Diuril and Dihydrochlorothiazide): These highly potent diuretic drugs have been shown to increase the effectiveness of the ganglion blocking agents when given in doses of the order of 1 Gm. per day.[18,69,77] Possibly they augment the action of reserpine and hydralazine, but the evidence is not yet convincing. This fact allows the physician to reduce the dosage of the blocking drugs to below the toxic levels and thus has greatly increased the ease with which these drugs may be given.

The best current evidence suggests that the loss of sodium in the urine with consequent reduction of blood and extracellular fluid volume is the mechanism behind the augmenting effect of chlorothiazide.[69] Whether these diuretics have any antihypertensive effect of their own is uncertain. If they do it is probably not great.

Chlorothiazide causes the loss of potassium as well as sodium, but the degree of potassium loss is much less than that of the sodium. If the drugs are given five days a week there is less danger of eliciting the syndrome of hypokalemia than when the drugs are given seven days a week. Liberal amounts of orange juice or, if truly necessary, commercial preparations of potassium salts may be used to prevent hypokalemia.

There is much yet to be learned about the mechanisms of the action of chlorothiazide and dihydrochlorothiazide, but there is no doubt of their usefulness. It may well be that they provide a simple way of taking an extremely low salt diet.

Dihydrochlorothiazide has recently been introduced. It is about ten times as active gram for gram as chlorothiazide, but qualitatively its actions seem indistinguishable from those of the parent drug. Since both are taken by mouth it makes little difference which one is used.

9. Antirenin: An antiserum for various species of renin has been prepared by Wakerlin and Johnson,[73] the active principle of which, "antirenin," neutralizes the acute pressor effect of the antigenic renin. The production of antirenin depends on the heterologous character of the injected renin. On the basis of their experiments, Wakerlin and Johnson treated hypertensive dogs with crude renin and showed that their blood pressure could be reduced. Inactivated renin did not do so. The fact that the antiserum titer of the dogs rose simultaneously with the reduction in blood pressure and fell more or less coincidentally with rise, suggested that antirenin was responsible. In one dog, however, the antirenin persisted in spite

of the rise in arterial pressure to the pretreatment hypertensive levels which speaks against this hypothesis.

Their observations have been further strengthened by their demonstration that daily intramuscular injections of renin into normotensive dogs prevents the development of hypertension when the renal arteries are constricted.[75]

More recent work by Wakerlin[74] suggests that the antirenin titer and the hypotensive effects of renin do not parallel one another, hence he has rejected his former explanation of his results. Goldblatt,[22] on the other hand, has repeated Wakerlin's work and believes that the antirenin hypothesis may be the correct one. Thus, further investigation is necessary to resolve the uncertainties. Like kidney extracts, antirenin is not to be considered a therapeutic agent. It is mentioned only because of its interesting possibilities.

10. Hydralazine (Apresoline): This agent has come into widespread use in the treatment of severe arterial hypertension. About 40 per cent of the patients respond favorably.[70] The effective range of dosage is from 200 to 700 mg. daily. We prefer to work the dose up to the maximum effective one, then reduce it 200 or more milligrams. A favorable response is reflected, not only in reduction of diastolic pressure to levels averaging less than 110 mm. Hg, but also in improved renal, cerebrovascular, and cardiac status.

Favorable responses seem more likely to occur in the hypertensives in whom the disease appears to be predominantly of neurogenic origin.

A few patients taking large quantities of hydralazine over a period of a year or more have exhibited an interesting syndrome which in its initial stages closely resembles rheumatoid arthritis. Later this syndrome may progress, if the drug is continued, to a febrile stage with signs and symptoms strongly suggestive of systemic lupus erythematosus. These manifestations are reversible on withdrawing or, in some cases, reducing the dosage of the drug.

If it is shown that hydralazine elicits a reasonable fall in arterial pressure, one of several other drugs may be combined with it, provided the other drug has also been shown to have some effect.[63] So far no one has proved synergism to exist among any of the drugs currently in use. Additive effects are common if both drugs are active. The fallacy in the use of multiple drugs is in continuing to pay for, and administer, drugs that are inactive in a particular patient. I have repeatedly pointed out that only a certain proportion of hypertensive patients respond to a single drug, diet, or surgical procedure.

One of the worst abuses is prescribing capsules or tablets in which several antihypertensive drugs are mixed. Not only is it impossible for the ineffective drugs to be eliminated, but the dosage of all the drugs is fixed as well. This leads to the poorest sort of therapy.

11. Ganglion Blocking Agents (Ganglioplegics): Over the years a great number of ganglioplegics have been introduced into commerce. They all have fundamentally the same action of partially blocking transmission of nerve impulses through ganglia. Both sympathetic and parasympathetic

ganglia are concerned, hence the difficulty in the clinical use of these drugs.

The introduction of chlorothiazide has greatly simplified the problem because it is now possible to use dosages of ganglioplegics well below those formerly necessary to achieve an adequate blood pressure-lowering effect. Despite active investigation and the production of many new ganglioplegics, there has been relatively small improvement in the properties of these drugs. Three of them, chlorisondamine (Ecolid), mecamylamine (Inversine) and pentolinium (Ansolysen) are now most widely used. They have the questionable advantage over the older hexamethonium in requiring much smaller dosage and the real advantage of better absorbability, thus making them somewhat easier to handle in practice. Dosage is entirely dependent on the degree of blood pressure reduction desired. We prefer to have the morning pressure just above that necessary to prevent the patient's fainting on arising from bed or on short, quiet standing The dosage must be constantly adjusted to the individual patient's needs There is no such thing as a "standard dosage."

The dosage is usually adjusted during the patient's stay in the hospital or in the out-patient department. Our patients usually then take their own blood pressure at home and keep us advised of the levels so that adjustment of the dosage is possible.

Patients and their families should be warned of the possible dangers from falling to the floor or ground during attacks of severe hypotension. Despite these dangers, it is our opinion that patients do better when their blood pressure is kept as low as possible but consistent with reasonable ability to walk and stand.

The ganglion blocking agents may be used by mouth or by subcutaneous injection, after a preliminary test dose by vein to ascertain sensitivity. In some patients, tolerance to the drugs appears; this may be dispelled by withdrawing the drug for two to three days.

Since the effects of the drugs on arterial pressure chiefly concern the postural reflexes, the head-up bed is used to take fullest advantage of the lowered blood pressure in the semireclining position.

The parasympathetic side effects, such as pupillary dilatation, dry mouth, urinary retention, constipation, obstipation, and finally, ileus, may be of such a degree as to become serious. Many of these can at least be controlled, if not abolished, by Urecholine or Myastenol.

12. Rauwolfia (Reserpine): The vasoactive alkaloid of Rauwolfia serpentina is reserpine. Recently it has been recommended and used for many of man's ills, including those of the mind. There is much to indicate that its effect is not simply that of a sedative.[68]

Given alone in doses of 0.5 to 1 0 mg. daily, it lowers arterial pressure in some patients; in a few it appears to do so almost specifically with arterial pressure returning to normal, but many patients receive no benefit.

The drug has some side, or toxic, effects. Nasal stuffiness, bad dreams, mental depression, and, rarely, parkinsonism seem to constitute the chief of these. Often added to other drugs such as hydralazine or hexamethonium, the latter may be reduced in dosage and equally good effects obtained. We do not consider reserpine a "wonder drug" but a very useful

one. While it appears to be most useful in those patients exhibiting much neuromuscular excitability, this is by no means either a sure or exclusive criterion.

A number of other reserpine-like substances have been isolated, and determined attempts have been made to show their superiority over reserpine itself.[43,68] Suffice it to say that so far none has been proved superior and despite much salesmanship none has received any wider usage. It would, indeed, be desirable to have a drug with less effect on cerebral function and more on blood pressure, but none has been found. It appears that such a drug will most likely be found by the synthetic organic chemist rather than those searching among natural products. A recent study shows that 26 per cent of patients receiving Rauwolfia experienced depression reactions.[60]

13. Treatment of Hypertensive Encephalopathy: Encephalopathy may occur in hypertensives from a variety of causes, chief of which are multiple small thrombi and vasoconstriction. While these are difficult to prove by rigid scientific analysis, still the evidence is strong in favor of at least these two mechanisms.[49] The first has no specific treatment. Anticoagulants have been suggested by some, but vigorously rejected as being detrimental by most others. Treatment of the vasoconstrictive type of encephalopathy, however, is highly satisfactory.

Often the period of encephalopathy is preceded by rising arterial pressure, headache of progressive severity, confusion and, finally, coma. The treatment we have found by far to be most satisfactory is continuous infusion of sodium nitroprusside.[50] The commercial salt is made up as a sterile saline stock solution (10 mg./ml.) and diluted as needed so that the drug can be administered at rates of 50 to 200 micrograms per minute. Blood pressure fall is very sharply defined with minute amounts of this substance. The infusion rate should be regulated so that arterial pressure falls to about 140/80 and remains there.

Often within a matter of thirty minutes the patient has aroused and in a few hours may be wholly recovered. During this critical period it is necessary to have the services of an alert nurse to maintain the proper flow of nitroprusside.

Ganglion blocking agents and reserpine have also been used parenterally for the treatment of acute encephalopathy.[49,50] The results may also be satisfactory, but *the problem of dosage is troublesome. Either too much* or too little may be given because there are no criteria on which to base an estimate of need. Whatever method of treatment is used, it is important to emphasize the necessity for early treatment. Prolonged neglect can lead to death, in contrast to the happy result when treatment is prompt and adequate.

14. Veratrum Alkaloids: Our experience with either the mixed or purified veratrum alkaloids has not been a happy one.[43] There is no doubt that a few patients respond almost specifically, but the proportion to those who do is relatively small. [illegible]
fall in arterial pressure, ou [illegible]
were so nauseated that they [illegible]

be said that many competent observers do not agree with our view on veratrum. We have seen little effect of chlorpromazine in reducing the vomiting threshold. Reserpine is said by Finnerty[17] to reduce the dose of Veriloid by one-third without loss of the effectiveness of either. This remains to be proved.

15. Adrenalectomy: This operation has shown beyond doubt that some forms of hypertension are abolished by removal of the adrenal glands. Administration of enough cortisone will restore the hypertension in most cases. So far, I have not been convinced that it should be used as a therapeutic tool except in those places especially skilled in the management of chronic adrenal insufficiency. The patient must also be intelligent enough to continue treatment and to recognize symptoms of insufficiency when they appear

16. Surgical Treatment of Hypertension due to Renal Artery Disease: The improvement in diagnostic technics has made precise anatomical diagnosis of renal disease possible.[59] For this reason, appropriate renal surgery may be carried out. This usually has consisted of segmental resection of the renal parenchyma, resection and anastomosis of the renal vessels, splenorenal anastomosis and homograft of the aorta with its renal vessels The results have been greatly improved as compared to those during the period when, without proper anatomical diagnosis, nephrectomy was done more or less indiscriminately.[16]

The indications we employ for the performance of angiography of the aorta and kidneys are:

1. Disparity in size or function of the two kidneys observed on the intravenous urogram.

2. Hypertension of unknown cause in patients under thirty-five years of age, with or without a family history of hypertension.

3. Hypertension that develops or becomes more severe after an attack of flank pain.

4. Malignant hypertension in any patient over sixty years of age.

5. Malignant hypertension of sudden onset in patients known to be normotensive recently.

Renal hypertensive patients respond to antihypertensive drugs in a satisfactory fashion. Surgical correction of the anatomical lesion, therefore, is not always advisable, especially because the rate progression of the lesion is usually not known. But the surgical technics of vascular surgery have so improved in the past few years that most serious consideration must be given this method of treatment.

Of 89 patients who we have recently studied,[52] fifty-nine were operated upon by Dr. Poutasse: nephrectomy was performed in thirty-eight, segmental nephrectomy in six, vascular surgery in fifteen, and thirty were treated medically. Arterial pressure returned to normal in thirty-one of the fifty-nine patients operated upon; seven obtained relief from diastolic hypertension, it was reduced in another seven, and unchanged in nine. Six patients died during the immediate postoperative period, and four much later from the prolonged results of atherosclerosis.

Renal arterial disease is sufficiently common to justify a much wider use of the current diagnostic methods than has heretofore been usual[30] Patients with demonstrable renal lesions need not all be operated upon, but they deserve the most careful appraisal of whether or not surgery would be desirable.

17. Treatment with Guanethidine: Guanethidine, a new type of antihypertensive drug, has been synthesized by Mull and his associates and studied clinically and pharmacologically by Page and Dustan[31] When given in doses of 25 to 150 mg. daily by mouth it elicits a slow but progressive fall in blood pressure. The dosage requirement is variable in different patients. Postural hypotension precedes the fall in supine pressure. Mild diarrhea is so far the only side effect noted.

The pharmacology of the drug is unusual in that it blocks the carotid occlusion reflex and causes immediate peripheral vasoconstriction, which is certainly not what one would want in an antihypertensive drug. But after administering it intravenously to animals, the pattern of response to a variety of pressor drugs suggests to us a reserpine-like action on the vessels with diminution of the available norepinephrine in the blood vessel wall.

While this drug has been studied on relatively few patients, the results are most encouraging.

18. Monamine-Oxidase Inhibitors: Ever since it was noticed that postural hypotension sometimes occurred when Marsilid was being administered, there has been some interest in monamine-oxidase inhibitors as antihypertensive agents. These drugs have the property of blocking the action of the enzyme which functions to destroy many of the pressor amines. It is not clear how prevention of the destruction of pressor substances elicits hypotension; rather the reverse would be expected.

The chief effect of these inhibitors certainly is elevating mood Depression is often relieved or abolished altogether. As in any other group of patients some of those with hypertension suffer from depression and for its relief the monamine-oxidase inhibitors are useful. As antihypertensive agents they have been disappointing, at least in our hands. Ten years ago, when few other antihypertensive agents were available, we used large amounts of Marsilid. Occasionally, evidence of early liver damage appeared and, further, the results were not impressive enough to arouse any enthusiasm. Subsequently, we have studied most of the newer inhibitors, but again we are unimpressed with them as antihypertensive drugs, although they are useful as antidepressants. Possibly, with further development of synthetic work on these drugs, the hypotensive properties can be intensified.

Postural hypotension is the common expression of the action of the monamine-oxidase inhibitor drugs with little effect when the patient is in the supine position. Fortunately, these drugs do not produce impotence, obstipation or mydriasis. Color blindness, however, may occur in as many as half the subjects. The dosage of one of the best of the amine-oxidase blocking agents, JB-516 or "Catron," is of the order of 10 to 30 mg. a day.

27

Arterial Hypertension

Incidence and Social Importance: Progress in preventive medicine and in the therapy of the infective diseases frequent in youth has greatly accentuated the significance of the chronic and progressive disorders commonly associated with senescence.[1,2] Of all of the degenerative diseases, cardiovascular disorders, hypertensive arterial disease, and arteriosclerosis, stand out as pre-eminently significant. Their significance is three fold (1) As causes of death; (2) as sources of protracted disability and invalidism; and (3) as challenges to medical science and practice because of the extreme complexity of their etiology and consequent ineffectiveness of anticipatory, preventive, and curative or controllative therapy.[3] Mortality data alone can be, and often are, seriously misleading. Incidence and the frequency, extent, and duration of disability are equally significant considerations from the viewpoint of scientific social medicine.[4] To illustrate how mortality figures alone confuse the issue, one has only to think of hay fever or the common cold; their mortality is negligible but the sum total of impaired efficiency is immense.

Data anent mortality from any and all of the chronic progressive disorders characteristically associated with advancing age are more valid and adequate than the reported "facts" regarding incidence and disablement, but even so must be considered as only approximations. Though the methods of reporting the cause of death and the analysis of these reports by the Bureau of Vital Statistics have improved in the last few years, it must be emphasized that arteriosclerosis and/or hypertension are frequently *contributory* causes of death when the "primary" or immediately obvious cause (such as injury in a vehicular accident) is applied in tabulations. Thus, we are justified in assuming that the present mortality data reflect but a part of the true significance of these disorders for they reveal only those instances where arterial disease was the primary cause of death. Even without the above considerations, the magnitude of the problem of arterial disease as a cause of death is startlingly impressive.

In 1953 (the most recent fully analyzed data), cardiovascular disease accounted for 52.3 per cent of all deaths at all ages in the United States. Arteriosclerosis and hypertensive disease caused 93.3 per cent of these cardiovascular deaths, according to statistics prepared by the Biometrics Research Section of the National Heart Institute and the Statistical Section of the American Heart Association. Hypertensive disease, either alone or in combination with arteriosclerosis is reported to have accounted for

42.6 per cent of cardiovascular deaths or 22.3 per cent of the total of the national mortality.

Data regarding incidence or morbidity of both arteriosclerosis and hypertensive disease are far more inaccurate and misleading. Almost all previous estimates of the prevalence of these conditions are based on samplings which revealed at most only the known, discovered, diagnosed cases in which there had arisen symptoms of sufficient intensity to demand medical attention. Thus the many millions of unidentified instances are *not* included. This error is particularly significant in relation to these disorders because hypertensive disease and arteriosclerosis are essentially asymptomatic in their early course and therefore a great many people are not aware that they are ill. Only by accurate survey, involving actual physical examinations, can truly reliable figures be obtained, and thus far this has not been done. The millions of examinations carried out by the Selective Service should be an immensely valuable source of information, but unfortunately, the screening examinations were so superficial, so hasty, and inadequate that the statistical interpretations are of dubious value. For example, it has been reported[5] that arterial hypertension was found in 2.9 per thousand White boys aged eighteen and nineteen and in 9.4 per thousand Negro boys. Later reports placed the prevalence of hypertension in selectees (1942-1943) at 18.4 per thousand, or 16.7 for Whites and 27.5 for Negroes[6] It has been conservatively estimated that approximately 4.6 million persons in the United States have hypertensive disease whether they know it or not. The number of impending, potential, or borderline early cases is probably even larger. In many respects the undiscovered instances of both hypertensive disease and arteriosclerosis constitute the greatest challenge to the medical profession, for the earlier in their typically progressive course therapy is instituted, the better are the chances of significant accomplishment.[2,7]

NORMAL ARTERIAL TENSION

Terminology: By the term arterial tension we mean the degree of pressure of the blood within the arterial walls. Hypertension exists when this pressure is unduly elevated; hypotension exists when it is abnormally low. Synonymous with the term arterial hypertension are high blood pressure, arterial hypertonia, and hyperpiesis. By common, but rather careless, usage, the term blood pressure has come to mean arterial pressure, though it is equally applicable to venous or capillary tension. The terms arterial tension, arterial hypertension, and arterial hypotension are preferable to the terms normal, and high or low blood pressure because they emphasize the role of the arterial structures. The blood is essentially a passive medium; changes in tension result from changes in the vessels.

As the pulse is a wave, initiated by contraction of the left ventricle, two levels of arterial tension are manifest: the *systolic* and *diastolic pressures.* The systolic tension represents the maximum pressure within the arterial tree at the end of cardiac systole; the diastolic tension equals the pressure in millimeters of mercury during the period of cardiac relaxa-

tion. The diastolic pressure thus expresses the *peripheral resistance*. It is the chief index of arteriolar tonus; if raised by arteriolar constriction, the greater cardiac force and elevated systolic pressure are compensatory. The difference between the systolic and diastolic pressures is known as the *pulse pressure*. The term "*differential tension*" is applied to asymmetry of the blood pressure as between the two arms or between the arms and legs.

It has become the convenient custom to record observations of the arterial tension as fractions: 120/70 representing a systolic tension of 120 mm. of mercury and a diastolic tension of 70 mm. In this instance the pulse pressure equals 50 mm.

Technic of Determination: Determination of the arterial tension is a simple procedure, but one which must be carefully and properly done to yield correct results. To determine the intra-arterial tension without puncture of the arterial tree involves an indirect technic. The flow of blood is halted by compression of the arm with an inflatable rubber cuff attached to a manometer calibrated to read in millimeters of mercury. As the pressure in the sleeve is reduced, the examiner listens for the first sound below the cuff in the cubital fossa. Just as soon as the constricting pressure equals that of the arterial blood, the interrupted flow of blood will be resumed and the dilation of the collapsed wall will be audibly discernible by the use of a stethoscope. At the moment the first sound is heard, the manometer registers the systolic pressure. The diastolic tension is determined by a characteristic *change in note* of the pulsation below the constriction. It was formerly held that the diastolic tension was to be determined at the moment of disappearance of all sound, but this has been proven to be incorrect.

Five distinct phases of sound are recognized as occurring upon deflation of the constricting cuff. These vary considerably in both duration and character. (1) First are heard sharp staccato, clicking sounds, the first of these occurring synchronously with the systolic reading. These are followed by a hissing murmur (2), soon to be replaced by soft thuds (3), gradually becoming heavier in tone, until (4) suddenly the sounds become softened or muffled, and then abruptly cease altogether.

The sounds of the first phase result from the first pulsation of blood in the artery under the stethoscope. The note is sharp and clear, the first often being louder than the others. The second phase is usually longer than the first. Hemic whorls and eddies are probably responsible for the hissing note obtained; these sounds are transitory, if partial compression of the cuff is maintained at this pressure for about fifty seconds, the murmurs disappear. Even with the usual rapid deflation, a phase of silence may occur, known as the "*auscultatory gap*." This gap occurs only in patients with hypertension or aortic valve lesions.

The thuds of the third phase arise from the arterial wall which is stretched between each period of collapse. The more rapid and tense the arterial wall, the sharper the note. High viscosity of the blood, as occurring in polycythemia vera, produces a *dull, sticky*, much muffled sound. The muffling of these thuds at the fourth phase appears when maximal

filling and collapse of the artery cease. It is at this point that the diastolic tension is to be read.

It is essential that the patient be in a comfortable, relaxed position when the arterial tension is to be determined. The cubical fossa must be bared, permitting the stethoscope to be placed upon the skin directly over the brachial artery, with the hand in supination. A major source of error in blood pressure determination is marked prolongation of the period of constriction; prolonged constriction with the inflated cuff causes a compensatory rise in the arterial tension.[8] Therefore, accuracy requires speed; it is wiser to take two or three rapid readings, taking the mean of the observations, than one slow, prolonged observation. Prolonged constriction also becomes distressingly uncomfortable and thus, through psychic stimuli, alters the arterial tension. Failure to observe an auscultatory gap by not making the primary constriction to a sufficiently high pressure may be a source of grave error. Fright or anxiety during the examination may lead to marked alterations in arterial tension. In young people, the chief source of error in blood pressure readings are nervousness and excitement.[9] Compression of the popliteal artery by sitting with the knees crossed appreciably raises the systemic blood pressure.

Normal Arterial Tension: The definition of normal is difficult; the term means different things to different people. If normal is taken to imply the range about the statistical mean, a wider range of variation is permissible than if the term is used to denote superior or desirable. To avoid confusion and misunderstanding of what follows, the term normal will here apply to average or mean levels commonly observed, but not necessarily optimum or wholly desirable. Actually normality is more nearly synonymous with mediocrity than it is with superiority or optimum.

Neither optimum nor normal are precise fixed points upon the scale of pressures. Both are best expressed as maximum or minimum ranges. These gradually rise with advancing age. At *birth*, the normal observed systolic tension varies between 35 and 55 mm., whereas in *infants* up to two years it averages 80 mm. The systolic tension in infancy is in direct relation to the weight, increasing as weight is gained. During *childhood* the arterial tension is variable, the gradual childhood rise ceasing at approximately eighteen years of age. In *healthy adults* the optimum arterial tension ranges from 110 to 140 mm. systolic and from 70 to 90 diastolic, gradually rising to the higher figures with increasing age. The rise in normal, as indicated by the recent extensive studies of Master, Garfield, and Walters,[10] is considerably greater. They define the range of normal arterial tension as 100 to 130 systolic and 60 to 85 diastolic at age twenty-two, to 117 to 175 systolic and 70 to 100 diastolic at age sixty. However, it has been demonstrated conclusively that levels of arterial tension above 140 systolic and/or 90 diastolic are associated with mortality rates higher than the expected rate.[11,12] After age fifty, a slight rise in systolic tension is not undesirable, but in those of optimal health for age, the diastolic tension tends to fall somewhat.[13] The normal diastolic tension does not increase with age. Hypertensive disease must be considered in terms of diastolic hypertension, not merely systolic pressure changes. There is no sharp, fixed point of division between the normal and abnormal.

Variations: Two groups of factors affect variations in the arterial tension in the absence of disease: (1) Constitutional factors producing continuous variation, and (2) psychophysiologic factors inducing transient fluctuations. Age is the most significant variable of the first type. Other constitutional factors that affect the normal range are sex, race, physique, and climatic environment. Prior to the climacteric, the blood pressure of women averages 2 mm. Hg lower than that of men of the same age. The effects of race are inseparable from the role of physique. In Asiatic and Oriental races, the normal blood pressure is from 10 to 20 mm. lower than in Caucasians; the former racial groups are of smaller stature. Arterial tension tends to increase with weight; average in heavier individuals is as much as 10 mm. higher than the mean. The very slender average lower pressures. Residence in the tropics is associated with a lower average blood pressure, although hypertensive disease is not uncommon. In the tropics, the arterial tension of northern white men falls 10 to 15 mm. It is uncertain whether this is due solely to the climatic factors; the tempo of life in the warmer climes is more leisurely. Increase in altitude or low barometric pressure has no constant effect upon the arterial tension. Abrupt chilling, as in immersion in cold water, may cause a considerable acute transient hypertension.

Sources of transient variations include emotional reactions, muscular work, pregnancy, posture, and changes in metabolic rate and in cardiac vigor. Posture of the arm effects the blood pressure determination; it is reduced by hyperabduction.[14] During sleep the arterial tension falls, the maximum fall occurring during the first two hours. This fall may be as much as 20 to 30 mm. When sleep is restless, or dreaming active, there may be an associated marked elevation of tension. Emotional reactions are the most significant source of transient physiologic (nondisease) variations in the arterial tension. Fear, anxiety, anger, and annoying discomfort are particularly potent sources of transient hypertension.[9,15] It is characteristic that the first readings of the tension of a new patient are as much as 20/10 mm. higher than those observed at later consultations because of subtle apprehension and or embarrassment at the time of the first visit. These fluctuations are often greatly exaggerated in hypertensive patients[16] Grossly increased rise in tension induced by emotional stimuli is evidence of unusual vasomotor lability and indicates vulnerability to the development of hypertensive disease. Such patients are potential hypertensives.[9,15,17] An isolated observation of hypertension does not justify any diagnostic conclusions. Repeated observations are necessary.

A too frequent source of gross error in circulatory evaluation is failure to observe the arterial tension in *both arms*. Asymmetry of the arterial tension or differential tension is not uncommon.[18] Significant differences in the two arms have been observed in approximately fifteen per cent of adults. It is commoner in hypertensive persons Cervical rib,[19] aortitis, anomalies of arterial development, intrathoracic lesions (neoplastic), cerebral lesions with trophic changes, and injury to one extremity all have to be considered.

Determination of the arterial tension in the lower extremities is *often of* great diagnostic import. Much more accurate observations are obtained

with the use of a special wider (18 instead of 12 cm.) cuff.[20] Normally the pressure in the thigh is higher than in either arm. When it is not, and especially when it is lower, such conditions as coarctation of the aorta,[21] occlusive disease, extrinsic compression or aneurysm of the descending, thoracic, or abdominal aortic or iliac arteries must be considered. Congenital coarctation of the aorta should be suspected immediately as a cause for hypertension in the upper extremities when the pressure is found to be high but not progressively increasing in a young person apparently free of renal impairment.[16]

Mechanism: The intravascular pressure is a reflection of several forces The propulsive force of the contracting left ventricle is opposed by the *peripheral resistance* of the vascular tree and the inertia of the blood. Alterations in the arterial tension are reflections of changes in the peripheral resistance and the efforts of the heart to overcome these. The diastolic tension approximates the peripheral resistance, the systolic tension equals this plus the cardiac force in systole. As the diastolic tension rises, so must the systolic tension; the cardiac burden is increased. This accounts for the much greater variability of the systolic pressure.

The peripheral resistance to the circulation is dependent upon a number of factors. One factor is the viscosity of the blood, which is chiefly dependent upon the cell count, the viscosity of the plasma being relatively low. The viscosity of the blood rises rapidly with cell counts exceeding 5,000,000 erythroplastids per cubic millimeter. Changes in the viscosity are of significance only in the rarer instances of polycythemia.

The most important, and also most variable factor, affecting peripheral resistance is the tonus and elasticity of the walls of the smaller arteries. This depends primarily upon the degree of arteriolar constriction. Hypertension is an arteriolar disorder. The arterioles are the primary site of disease in hypertensive disease. Arterioles have a threefold function: In common with all blood vessels, they act as conduction ducts; they also control the distribution of blood to various parts of the body by appropriate relaxation or constriction in areas of increased or diminished work, respectively; and they act as a dam with sluice gates to control the head of pressure in the circulatory system. The walls of these smaller arteries consist chiefly of spirally-arranged smooth muscle fibers, under direct control of the sympathetic nervous system.[8]

The average caliber of the vast numbers of small arteries and precapillary arterioles is responsible for most peripheral resistance. Constriction or relaxation is dependent upon the constant flow of impulses along the sympathetic nerve fibers to the smooth muscle of the arterial walls. Fluctuation in the intensity of these stimuli and in the resultant vascular tone control the diastolic arterial tension. The vasomotor nerves contain both dilator and constrictor fibers and ramify throughout the vascular tree even unto the capillaries. The vasomotor nerves are derived from the anterior spinal roots from the first thoracic to the fourth lumbar segment. The vessels of the head, neck, and extremities are innervated by fibers from the cord; the whole apparatus is to some degree controlled by a medullary center, both through the cord and the vagus nerve. There may

be reflex reactions through the sympathetic system without apparent cord connections.

The tonus of the arterial system is normally labile and in constant homeostatic flux and adaptation for such factors as local demands for hyperemia under increased functional activity. Substances such as epinephrine, angiotonin, pituitrin, the nitrites, and many other pharmacologically active principles, markedly alter the arterial tension through change in the sympathetic stimuli to the smaller arteries.

The whole equilibratory mechanism is also intimately correlated with the control of cardiac activity through the depressor fibers of the vagus nerve. Rise in arterial tension results in retardation of the cardiac rate and, conversely, a marked fall in the arterial tension causes cardiac acceleration. Direct stimulation of the arteriolar muscles may occur without nervous intervention. The effect of angiotonin and of certain bacterial toxins in causing vascular constriction occurs in vessels entirely freed from their innervation. This elaborate and intricate mechanism to maintain a constant vascular equilibrium and relatively stable intra-arterial tension is in constant activity. Relaxation at any one point is immediately compensated by constriction elsewhere, and *vice versa.*

Hypertension, then, represents an imbalance of circulatory homeostasis. It does not involve new mechanisms and is not a new phenomenon, but merely a deviation from the normal plane of equilibrium. The imbalance is purely *quantitative;* no new *qualitative* elements are requisite. As a clinical phenomenon, therefore, hypertension is comparable to fever; like fever, it is not a disease but a state of *disturbed physiologic balance.* Care must be exercised to distinguish the *hypertensive state* from *hypertensive disease;* hypertension is but a symptom of the latter.

A state of hypertension may arise temporarily from any of many sources; fear, anger, effort, or acute intoxication (such as in eclampsia or acute uremia poisoning). With the exception of the increased tension observed in coarctation of the aorta, however, hypertension invariably results from constriction. Arterial hypertonia may be a purely compensatory phenomenon It is characteristic of physiologic reactions, however, that they often exceed requirements in both intensity and duration. Most compensatory reactions, such as fever, leukocytosis, or edema, tend to subside with the termination of stimulation. Arterial hypertonia, which may be induced as a physiologic response to the need for a greater renal blood flow,[16] tends to be persistent and progressive rather than self-limited. Thus the physiologic state of hypertension may by prolongation become the progressive degenerative disorder, arterial hypertensive disease.[22] As the disease progresses, the "symptom" hypertension becomes more persistent and more pronounced, because of the changes in the arteries. The hypertension is, however, still a symptom and must not be confused with the disease *per se.*

HYPERTENSIVE ARTERIAL DISEASE

Despite the vagueness of onset and haziness of the line between physiologic state and disease in hypertension, hypertensive arterial disease is a

true clinical entity with a characteristic pathogenesis and course. The etiology of any disorder is perhaps the most important facet of the problem from the clinical viewpoint, for effective therapy, whether preventive or curative, invariably is based upon removel or amelioration of causative influences. The etiology of hypertensive disease is extremely complex, involving multiple superimposed factors which vary in each individual instance. But the mere fact that causation is not always apparent is no justification for failure to search for all possible factors. The terms "idiopathic," "essential," "functional," and/or "benign" hypertension are to be deplored, as they imply the etiologic study of the individual patient is futile.

Hypertensive arterial disease is a slowly progressive disorder characterized by an asymptomatic early course, a complex and variable etiology, but a remarkably consistent pathogenesis. The consequences of hypertension, including symptomatology and subtle physiologic impairments, are also variable. As a result, each instance of the disorder must be considered as a highly individual problem. Making a routine of therapy is dangerous; no two cases have necessarily the same etiologic background or same consequences. Individualization in diagnosis and therapy is essential.[23]

The almost invariable overlapping of several of the progressive chronic disorders so frequent in senescence introduces another significant element into both diagnosis and therapy of hypertensive disease.[24] The whole group of disorders which are conveniently but inaccurately called "degenerative" overlap one another. Admittedly diabetes mellitus, arteriosclerosis, hypertensive disease, chronic nephritis, the anemias and the like are clinical entities, but they are so frequently superimposed in the same patient that sharp diagnostic distinctions become absurd. For example, as we shall see later, hypertension, if longstanding, invariably leads to myocardial damage and, usually, both renal and hematopoietic impairment. It is therefore imperative that in the diagnostic study of hypertensive disease thorough functional evaluation of reserve capacities be included.[23,25] The glucose tolerance test and renal functional tests, together with study of the cardiac functional capacity, may be just as significant in guiding wise therapy as measurement of the blood pressure. This is particularly significant if the physician is more concerned with treating the patient who is ill than in merely treating the disease.[3]

The degenerative diseases present a common denominator in that all of them induce interference with the nutrition of parenchymal cells through changes in the intercellular matrix. Nutrition is much more than the ingestion of proper foods; it involves transport and utilization.[26] The internal milieu is the medium through which cells are maintained. Circulatory disorders may affect the cellular nutrition in any one or more of four ways: (1) Inadequate nutritional supply; (2) inefficient distribution; (3) ineffective utilization of food elements, and (4) accumulation of noxious metabolic debris. Thus, hypertensive disease may impair glucose metabolism by reason of histanoxia of the islet tissue in the pancreas; may reduce renal efficiency and thus induce azotemic intoxication. The individual variations in the distribution and intensity of arteriolar damage in

hypertensive disease are as yet unexplained, but they account for the great variability of physiologic consequences observed As hypertension and arteriosclerosis are both related to the fundamental phenomena of senescence[1,7,27] the element of variability in lesion distribution and intensity probably depends upon similar factors: no two individuals are subject to identical series of insults and injuries. The accumulative effects of the innumerable intoxications, transient infections, psychic and somatic traumata which constitute the vicissitudes of living, probably play a major role in determining the vulnerability of this or that structure or tissue[7]

Diagnosis in hypertensive disease must be much more than merely identification and labeling of a disease state. Diagnosis, which exists primarily for the purpose of guiding therapy, should include several elements if it is to be fully useful. Diagnosis involves: (1) Identification of the disease state; (2) determination of the etiology of the disorder in the individual; (3) evaluation of the severity of the disorder, including functional depreciations; (4) estimation of the rate of progression of the disorder, and (5) discovery of complicating dysfunctions which affect the health of the individual patient. In other words, we need to know the answers to: What is it? Why is it? How bad is it? And, how fast is it? Any diagnosis which ignores one or more of these pertinent queries is incomplete. A diagnosis is always only an opinion and is therefore to be left open to revision.

Pathogenesis: Hypertensive arterial disease starts with continuation of arteriolar hypertonia. This hypertonia may result from anything which stimulates or irritates the arteriolar musculature for any length of time. The sources initiating irritation are many; they will be discussed shortly. If the stimulation is persistent, continuous hypertonia results and hypertrophy of the medial muscle tissue follows due to increased work. This hypertrophy adds further constriction; the same degree of nervous stimulation produces a much more energetic response from the hypertrophied muscular walls. Muscle fibers are not adapted to continuous load or effort. Fatigue slowly ensues as the next phase of the slowly progressive steps of pathogenesis. Fatigue reduces the threshold of stimulation; causes hyperirritability. Fatigue is not to be confused with exhaustion; with exhaustion, response to stimuli ceases.

Thus, a vicious circle is engendered. This may be considered as a "perpetuating factor in hypertension," in contrast to the "initiating factors" of primary arterial irritation.[8]

Certain arteriolar muscle fibers, unable to maintain the continuous effort, become exhausted. Exhaustion and degeneration of these cells permit of their replacement by collagenic connective tissue. The replacement of the muscle tissue by connective tissue fibers is not an aggressive or invasive process on the part of the latter tissue; it is essentially a protective mechanism by which the tottering exhausted muscular structures are being replaced and supported by a scaffolding of connective tissue. Gradual continuation of this process results in arteriolarsclerosis or fibrosis. Arteriolarsclerosis, with rigid, narrowed arteriolar walls, is the endpoint of the pathogenesis of hypertensive arterial disease.

The steps of development are simple: arterial muscular irritation causes relatively continuous arteriolar hypertonicity; this, in turn, produces medial muscular hypertrophy, more spasticity, fatigue and hyperirritability, perpetuating the process, and exhausting the muscle cells, ultimately resulting in fibrotic replacement of the muscle. This process is insidiously slow, often requiring many years before severe sclerotic changes are manifest, but is also dreadfully persistent.

The anatomic pathologic changes observed are the *result* rather than the cause of arterial hypertension. Arteriolarsclerosis is the ultimate sequel of arteriolar spasm. But it is not due to the increased pressure of the blood, for these changes do not occur in the small vessels of the arms and upper chest in coarctation of the aorta, despite long-continued high blood pressure. In aortic coarctation there occurs no arteriolar hypertonicity. Renal injury is not invariably notable even in extreme instances of hypertensive arterial disease. Renal disease may or may not be associated with arterial disease, and when hypertension does occur coincident with nephritis, the arterial changes are of the same nature as in those instances essentially free of renal disturbances. Arterial hypertension exacerbates and accelerates degenerative changes in the larger vessels, but does not initiate such changes. It must be constantly kept in mind that the vascular disease directly associated with hypertension involves only the smaller arteries and arterioles, arteriosclerosis of the larger vessels is an independent entity though the two may, and often do, coincide.

Etiology: Causation is never singular, but a combination of factors In hypertensive arterial disease, as well as with the other chronic progressive disorders associated with later maturity, the great multiplicity of factors involved and the fact that often these influences may have initiated the disorder several years before the patient is observed make individual etiologic analyses extremely difficult. In no two instances are the combinations of insults or stimuli necessarily identical; most frequently several factors are superimposed. To some this problem has seemed insurmountable, and to avoid the obligation of search for causative influences they have declared the cause to be wholly unknown and labeled the disorder either "essential" or "idiopathic" hypertension. Others prefer to divide hypertension into two major forms: "secondary," where the etiology is known or suspected, and "essential," where it is admittedly unknown[28] However, though there is much we do not as yet understand anent the causation, we must not assume that the unknown is unknowable; constant search and research will ultimately solve this immensely important problem. And every patient with hypertensive arterial disease is an individual problem in clinical research.[29,30,31]

Causative influences are amenable to analysis. They fall into three categories: *Predisposing, provoking,* and *perpetuating* factors. These three forms of etiologic forces are present invariably in the causation of any and all illness, although they are not necessarily of equal importance or weight. The provoking factors in hypertensive disease may be *anything which over a long period of time stimulates contraction of the arterioles of a vulnerable individual; vulnerability is a predisposing factor.* Obviously, such a

definition of etiology demands amplification. However, three significant implications warrant emphasis: (1) The great multiplicity of possible causative factors; (2) recognition that considerable duration of irritation is essential, and (3) the importance of vulnerability. It is possible to classify the many sources of vascular irritation in several ways, but from the viewpoint of clinical application, classification based on the three types of etiologic influences enumerated above appears to be the most practical.

The Commoner Etiologic Factors in Hypertensive Disease

I. Predisposing Factors (affecting vulnerability)
 A Hereditary
  1. Constitutional vasomotor instability
  2. Constitutional emotional instability[17,32,33]
  3. Constitutional endocrine imbalance[34]
   a Thyrotoxic (apprehensive) constitution
   b. Virilescence
   c. Diabetic potentiality
  4 Anatomic anomalies
   a. Vascular anomalies
   b. Renal dwarfism, polycystic kidneys, etc
 B Prior Injuries
  1. Prolonged emotional turmoil (fatigue)[5,17,33]
  2. Accumulative injuries from various intoxications
  3 Accumulative injuries from various infections
  4. Accumulative injuries from various nutritional deficiencies and excesses

II Provoking Factors
 A. Psychosomatic; anxiety, prolonged[9,15,17,33]
 B Intoxications
  1. Endogenous
   a Renal, bilateral nephritides
   b Renal, unilateral hydronephrosis[41]
    Renal, unilateral pyelonephrosis
    Renal, unilateral circulatory obstruction
    Angiotonin pressure effect[28,30,31]
   c. Anemia
   d Fatigue
   e. Pregnancy[35]
   f. Inadequate fluid intake
  2. Endocrine
   a. Gonad involution, climacteric[36,37]
   b Diabetes mellitus[38]
   c Hyperepinephenemia; medullary adrenal tumor, pheochromocytoma[39,40]
   d Pituitary basophilism
  3. Exogenous
   a Metallic poisons (As, Pb, and Hg)
   b Habitual excesses condiments[8]

4. Infections
   a Focal infections, long duration
   b. Systemic infections (especially virus influenza) and typhoid fever
5. Neurologic lesions[31]
   a Increased intracranial pressure
   b. Brain tumors

III. Perpetuating Factors
   A. Inherent in pathogenesis
   B Continuation provoking factors
   C Superimposition new provoking factors
   D. Progressive renal functional impairment due to hypertension[41]
   E. Progressive cerebral impairment

This outline is admittedly incomplete. There are many causative factors in hypertensive disease. Vasomotor control is maintained by both humoral and nervous mechanisms.[42] There are many instances of hypertension in which findings suggestive of renal ischemia cannot be demonstrated pathologically,[43] physiologically,[44] or urologically.[45]

Correction of etiologic factors is requisite for successful therapy. Many of those identified in the outline are amenable to therapy; others are irrevocable; still others are as yet unidentified. *Anything which persistently irritates the arterioles in vulnerable individuals and so initiates the pathogenic processes by arteriolar hypertonicity may set in motion the development of hypertensive arterial disease.* Once so started, the perpetuating factor of arterial fatigue perpetuates the development, which continues even though the original factors have ceased to exist.

Classification: For practical purposes, the simplest classification is probably the most useful. Hypertensive arterial disease may be seen early, at which time it is "*spastic*," with wide variations of the tension on different occasions, due to marked changes in the arterial tonus; it may be seen late, when it is "*sclerotic*," with relatively fixed diastolic tension due to the fibrotic changes in the arteriolar walls. Between these two extremes is a long intermediate period, when both spasm and sclerosis are present. These three types are not different forms of arterial disease, but different stages of the same disease process. Hypertensive arterial disease may or may not be complicated by associated disease, such as nephritis, diabetes mellitus, cardiac disease, lues, thyrotoxicosis, or pregnancy.

In certain instances, for reasons not well understood, the progression of the arterial disease is markedly accelerated; degenerative changes appear very early and progress is rapidly downward. To this group, the term "*malignant hypertension*" has been applied. The processes are essentially the same as in the more usual slowly progressive hypertensive arterial disease, only the rate of progression is increased. As yet no adequate explanation of this has been presented.

The following classification of arterial hypertension is presented because of its simplicity, adaptability to clinical application, and physiologic and pathogenic basis.

CLASSIFICATION OF ARTERIAL HYPERTENSION

I. Hypertensive Arterial Disease
  A. Usual Form ("Essential hypertension")
    1. Potential Stage
    2. Spastic Stage
    3 Intermediate Stage
    4. Sclerotic Stage
  B. Special Forms
    1. "Malignant" or Rapidly Progressive Form
      (Cause of accelerated progress unknown)
    2. Hypertensive Arterial Disease with Complications such as:
      a. Nephritis
      b. Cardiac disease
      c. Arteriosclerosis
      d. Diabetes
      e. Syphilis
      f. Plumbism, etc.
    3. Hypertension in Pregnancy[48]

II. Hypertension without Hypertensive Arterial Disease
  A. Arteriolar Constriction (Transient), such as due to:
    1. Cold
    2. Emotions (fear, anger)
    3. Intoxications
    4. Increased cerebral pressure (brain tumors)
      (*Note:* Hypertensive state often precursor of hypertensive arterial disease)
  B. Anatomic Anomalies
    1. Coarctation of aorta
      (Hypertension found in arms only, no arteriolar constriction)
    2. Aortic regurgitation (systolic only)
    3. Cervical rib (asymmetric)
    4. Aneurysms (asymmetric)
    5. Thyrotoxicosis (systolic only)

The stage of development of progressive hypertensive arterial disease is a significant factor in determining amenability to therapy and therefore prognosis. The identifying characteristics and pathologic changes of the four phases will be considered in the section on Prognosis.

Consequences of Hypertension. ***Symptoms:*** The most significant aspect of the symptomatology is the absence of symptoms early in the course of the disease. The gradual, though persistent, rise in the arterial tension, taking place over a period of years, is so insidious that compensation and readjustment can keep pace with the changes and no subjective phenomena are noted by the patient. It is remarkable, but not uncommon, that individuals may live for years with no feeling of discomfort or illness with blood pressures perhaps twice the normal. The absence of discomfort is in part responsible for the usual neglect of hypertensive arterial disease in its earlier phases. The objective evidence is always there for those who will take the trouble to determine the arterial tension. On discovery of

arterial hypertension, however, it is necessary to distinguish between a state of hypertension and hypertensive arterial disease. Any prolongation of the hypertensive state leads to the progressive disease. There is nothing typical in the appearance of hypertensive patients; obesity and undernutrition, irascibility of temper and phlegmatic stoicism, flushed facies and pallor are all seen with little difference in frequency.

Late in the course of the disease *subjective symptoms* develop; these result indirectly from the failure of parenchymal functions because of impaired and inadequate blood supply. With one exception, all the deleterious consequences of prolonged arteriolar constriction are due solely to the interference with the flow of blood *distal to the constriction.* This exception is the increased burden of work put upon the left ventricle. The location, acuteness and intensity of local circulatory impairment determine the symptoms. The sequelae may be due to either: (1) Chronic and accumulative ischemia, or (2) acute or abrupt irregularities of the blood supply. Among the latter are included such dramatic sequelae as apoplexy, angina pectoris, retinal hemorrhages, and coronary occlusion with myocardial infarction. Though these "accidents" are abrupt, it must not be forgotten that the insidious and progressive changes are long standing. Symptoms may be of sudden onset; the disease is not.

Depreciations in functional capacities must be measured to be detected early. Symptoms appear only when the effective capacity is inadequate for the functional burden. *It is only under condition of stress that earlier diminutions of functional reserves are detectable.*

The consequences of arterial hypertensive disease fall naturally into three major divisions: (1) Those referable to cardiocirculatory failure; (2) those resulting from malcirculation in the nervous system, and (3) those arising from renal failure. There is nothing specific about the symptoms; they are manifestations of local circulatory failure.

Cardiocirculatory symptoms are of two types: (1) Those related to cardiac changes, and (2) those arising from changes in the peripheral circulation. The heart is an integral part of the vascular apparatus; the myocardium (media) is subject to the same injuries as the medial muscular layer of the arterioles. Furthermore, the cardiac burden of labor is greatly augmented by the markedly increased peripheral resistance. These two factors are sufficient to warrant the *a priori assumption that in every instance of hypertensive arterial disease of long duration some cardiac injury has occurred.*

Left ventricular cardiac hypertrophy occurs slowly in arterial hypertension; it is rarely marked. The second aortic sound becomes sharp and ringing but not necessarily louder. With the gradually progressing cardiac hypertrophy, the mechanical energy of the heart is enhanced. This, aided by reflex vagal influence, permits of a slow, firm, full, noncollapsible pulse As the burden of labor increases, and the heart is no longer able to cope with the intensified effort, dilation occurs. With dilation of the mitral ring, a soft blowing systolic apical murmur appears. This is due to the widening of the ring so that true approximation of the valve leaflets is no longer possible. The murmur of this so-called "relative mitral regurgita-

tion" is soft. At this stage of cardiac change subjective symptoms are not pronounced. Distress is induced by slowly diminishing degrees of effort. *Dyspnea* may at first be noted only on climbing stairs; later, a heavy meal, a cold wind, or the carrying of a package may induce unpleasant breathlessness. This diminution of the threshold is often so insidious as to pass unnoticed until some exceptional effort brings about acute distress. The degree of effort required to produce undue dyspnea is perhaps the best clinical criterion of the cardiac reserve strength.

Fluoroscopic examination should be included in the diagnostic study of all hypertensive patients. It reveals clearly the typical left ventricular hypertrophy and/or later dilation, and is most informative concerning the status of the aorta. In long-standing hypertension, the aortic knob is more prominent and often of greater than usual density. Severe hypertension without aortic-knob dilation is most probably recent; this observation is frequently the first clue that one is dealing with an early but rapidly progressing or "malignant" hypertension.

Dyspnea may or may not be accompanied by *precordial pain*. This may vary from mere heart consciousness to the extreme pain of angina pectoris. The degree of pain, however, is not a reliable criterion of the severity of the cardiac lesion. Angina pectoris and related phenomena are discussed elsewhere. As the cardiac reserve fails to meet the ever increasing demands for more and more work as the diastolic tension rises, the pulse increases in rate. The heart gradually becomes asthenic, having previously been hypersthenic. This early stage of cardiac decompensation, or lowered cardiac reserve, is most important. It is the warning of impending catastrophe; cardiac decompensation or defeat.

Cardiac failure, due essentially to exhaustion, causes more than half the deaths attributable to hypertensive arterial disease. Early evidences of such *cardiac fatigue* and lowered reserve are undue dyspnea upon minor exertion, pedal edema in the evening, rising pulse rate, subcyanotic color of the finger tips and lips, many vague and indefinite digestive disturbances, cardiac consciousness or precordial pain, vertigo and cephalalgia, and, lastly, a falling systolic tension without a corresponding reduction in the diastolic level. A blood pressure of 160/130 with the pulse at 110 is more cause for immediate alarm than one of 190/125, pulse 85. The left ventricle has become too exhausted to maintain an adequate pulse pressure.

Peripheral circulatory symptoms are: paresthesias, numbness of the extremities, transient edemas, and the characteristic "hot flashes" of the climacteric. Not infrequently, with potential arterial hypertension[9] and emotional instability, large urticarial blotches and exaggerated blushing are manifest.

Personality: The hypertensive personality is readily identifiable with experience.[10] An undue emotional instability is typical. These people are intensely ambitious and often reveal a singleness of purpose which leads to eminent success in their chosen careers. These personalities resent delay and inactivity; they are impatient to "do something" when matters go amiss. Chronic, habitual anxiety is frequent. Habitual worriers consti-

tute a large proportion of all hypertensive patients. Emotional calm is replaced by irritability, and petty annoyances are grossly exaggerated. A general restless mental activity prevails, generally futile, unstable, and fickle. A state of indecision, particularly if it must be concealed because of great pride, also characteristic of the hypertensive personality, is severely exhausting. Weiss[33] and others[9,32] have emphasized the importance of concealed unexpressible hostility and resentment in the etiology and the genesis of arterial hypertension.

Neurologic symptoms are frequent. Impairment of memory is common and, as in the senile, this impairment is most marked for recent events. Insomnia is frequently an annoying feature, principally manifest by a difficulty in getting to sleep. Morning cephalalgia, usually occipital in location, accentuates the sense of fatigue upon arising; the patients do not feel rested. The morning headache is generally transient, disappearing upon activity. Transient cerebral symptoms, such as asphasia, hemiplegia for a few minutes, amblyopia, amaurosis, or momentary loss of memory are a source of considerable anxiety. These transient attacks are associated either with an excessive rise in arterial tension, or with a transient fall in tension which produces a relative hypotension in the cerebral circulation. During such periods disorientation, delirium, or confusion are common, and parkinsonism may be simulated.

Peripheral neurologic symptoms involve chiefly the special sense organs. Tinnitus aurium occurs in about five per cent of cases. Disturbances of vision are common. Scotomata, blurring and haziness of the visual field, result from retinal malcirculation. Eyeground changes are said to be demonstrable in more than ninety per cent of patients with hypertension of more than ten years duration. Narrowing of the retinal arteries, flame-shaped hemorrhages, glistening, thickened tortuous vessels, and whitish exudates are all readily demonstrable by ophthalmoscopic examination.

Cerebral apoplexy with sudden loss of consciousness and complete or partial hemiparalysis is a dramatic and startling consequence. Hemorrhages occur through a sudden rupture of a degenerated cerebral vessel. The local arterial lesions, presumably miliary aneurysms, are the fundamental point of weakness. Apoplexy can occur without hypertension but not without local arterial disease. Arteriosclerosis without hypertension may so reduce cerebral blood flow that thrombotic occlusion occurs with almost identical consequences. Apoplexy during sleep or at rest may follow relative hypotension and thrombotic vascular occlusion. The majority of strokes are not fatal, although the hemiplegia may persist permanently, with first flaccid and later rigid paralysis. Hypertension may also be associated with the less dramatic but often more disabling encephalopathy due to repeated minor cerebral arterial thromboses or hemorrhages; the "little strokes" of Alvarez.[47]

Renal injury in hypertension may be of three types: (1) Primary and partially causative of the arterial disease; (2) secondary and resulting from the malcirculation due to the arterial disease, and (3) coincident, in which the renal and vascular structures have been injured simultaneously. Extended discussion of the etiology, mechanism, pathogenesis, symptoma-

tology, prognosis, and therapy of renal disease and renal decompensation does not belong here. Extensive impairment of renal efficiency is exceptional in hypertensive arterial disease. However, renal function studies are indicated in every case of hypertensive disease. Intravenous pyelography should be part of the minimum diagnostic study.

Prognosis: The average prognosis for hypertensive patients, has not been good. More modern methods of therapy, if instituted early in the course of the disease, have greatly improved this outlook In the evaluation of the prognosis in individual instances a number of factors must be given consideration.[48] Among the important factors affecting the prognosis in any specific clinical instance are: the age of the patient, the duration of the vascular disease, the rate of progression, the etiologic factors involved, the degree of permanent, irreparable arteriolarsclerosis which has occurred, the association with other complicating disturbances, such as cardiac or renal injury, diabetes or pregnancy, as well as the height of the diastolic arterial tension. As age increases, the life expectancy, of course, declines synchronously, but greater age at onset implies a slower progression and thus improves the prognosis.[49]

In general, the longer the duration of hyperpiesis, the greater the degree of arteriolar muscular exhaustion and replacement fibrosis or arteriolarsclerosis. Arteriolarsclerosis, however, does not progress with the same rapidity in all patients; frequently patients are encountered whose hypertension has existed for many years without appreciable sclerotic changes in their arterioles. On the other hand, evidence of marked sclerosis may sometimes be found within two or three years of the known onset.

The significance of the etiologic background lies in the varying degree to which various factors are amenable to therapy. If hereditary predisposition to premature vascular degeneration is conspicuously manifest in the family history, it is, of course, of no avail to hope for any change in the intrinsic constitution of the patient. On the other hand, should dietary indiscretions, thyrotoxicosis, obesity, plumbism, anxiety, or unilateral renal ischemia be significant in the etiology, their amenability to correction improves the outlook greatly. Removal of etiologic factors is the first principle of therapy. The *duration* of provoking factors is significant. Unfortunately, etiologic diagnosis is almost always fragmentary and largely presumptive. Nevertheless, every effort should be made to obtain all the information possible.

However, the most important factor in the evaluation of prognosis is the extent of permanent vascular injury and rate of progression. The pathogenic development from transient arteriolar spasticity to permanent collagenic scarring of the arteriolar walls is a slow, gradual, but persistent evolution. The patient may be seen at any stage. Therefore, to prognosticate properly, it is of the utmost importance to determine the phase of development. The rate of progression of arteriolar changes can be estimated only if one knows the approximate date of onset and the stage of the pathogenesis reached The former unknown is difficult to determine because of the silent and wholly asymptomatic early course. However, painstaking inquiry into the past history, including examinations for life

insurance and the like, frequently reveal some clues as to probable duration.

Evaluation of the stage reached in the pathogenesis depends upon the variability of the diastolic tension. Persistent diastolic hypertension is more significant than transient excessive hyperpiesis. Direct inspection of the retinal arteries by retinoscopy gives additional valuable data. However, these data may be misleading, for the fibrotic scarring proceeds at different rates in different parts of the arteriolar vascular tree. Identification of the four stages of hypertensive arterial disease is based upon the following tabulated criteria:

Stage	Clinical Phenomena	Pathology
1. *Potential Stage*	Undue lability of the arterial tension, excessive response to stimulation Normal retinal arteries; no cardiac enlargement, or evidence of impaired competence	None.
2 *Spastic Stage*	Continuous but variable hypertension; lability still marked; tension may be reduced *temporarily* by vasodilator drugs; white line and venous nicking seen in retinal vessels, moderate left ventricular hypertrophy; ECG left axis deviation, aortic knob slightly more prominent than before.	Hypertrophy of medial muscles of arterioles
3 *Intermediate Stage*	Diastolic tension elevated more and more persistently; lability diminished, hypertension due in part to hypertonia and in part to sclerotic narrowing; increasing left ventricular hypertrophy and dilation, lowering compensation with dyspnea after less and less effort; probable casts, few RBC etc. in urine.	Degeneration of media and replacement fibrosis in some arterioles, changes unequally distributed, thickening and fibrosis of intima with some permanent narrowing of vessels, medial hypertrophy continued
4. *Sclerotic Stage*	Diastolic tension quite rigid and high, secondary symptoms failure of various organs due to local histanoxia; sclerosis visible in retinal vessels, no longer amenable to therapy.	More generalized but still variable arteriolarsclerosis and endarteritic intimal fibrosis

Whether or not peripheral resistance is relaxable and to what degree it may be reduced may be determined quickly by the amyl nitrite test,[50] which is carried out as follows:

Amyl Nitrite Test: With the patient comfortable, either sitting or lying down, enough determinations of the arterial tension are made to obtain a fairly constant basal level. The patient then inhales twice of a freshly broken perle of amyl nitrite (0.3 cc. or 5 minims). Rapid observations of

the arterial tension are repeated until the ensuing fluctuations in tension have passed. The essential observation is the *minimum diastolic level*. This is usually observed twenty to forty seconds after the inhalation and characteristically just prior to the intense flush. A secondary rise in tension to levels equal or slightly higher than before the test occurs sixty to eighty seconds after inhalation. There may be some transient vertigo, palpitation, sense of presyncope, and rarely, headache. These are quickly relieved by a whiff of aromatic ammonia if they do not disappear spontaneously in a minute or so.

No ill effects follow this procedure. Although it might be argued that abrupt relative hypotension is hazardous and might induce cerebral thrombosis, it must not be forgotten that in patients with extensive arteriolarsclerosis no great fall in pressure occurs. Such relaxation does not and cannot occur where extensive arteriosclerosis exists. The degree with which diastolic tension approaches normal is a prognostic criterion of considerable moment, and also serves as an objective in therapy. The same information can usually be elicited by prolonged clinical observation, but the patient justifiably often demands a more immediate answer. The coincidence of the actual therapeutic results obtained with predictions made months earlier is very close. The amyl nitrite test truly reveals the amenability to therapeutic correction in individual instances of the disease.[51]

An adequate diagnostic study of hypertensive patients for guiding therapy and evaluating prognosis must include evaluation of both *cardiac and renal functional reserves* and search for complicating disease. The *cooperation of the patient* is important; hypertensive disease is *controlled* rather than *cured*. Observation and wise management must be continued for many years.

Treatment: It is essential that the fundamental principles of therapy applicable to chronic progressive disorders and realistic and pragmatic objectives and intentions be clearly comprehended by the physician. The implications of these principles and limited objectives must likewise be explained to the patient in such a manner that he (or she) understands what the physician is trying to accomplish, how he hopes to bring this about, and why there exist very decided limitations to what may be expected. Hypertensive disease is not curable in the same sense that lobar pneumonia, appendicitis, or a simple fracture is curable. However, the therapeutic objectives of anticipation,[51] prevention, retardation of progression, control,[52] and long postponement of disablement are feasible, realistic and appropriate. In advanced hypertensive disease, with considerable arteriolarsclerosis, arrest of progression and the maintenance of the *status quo* may be the maximum therapeutic accomplishment possible; it must be explained that such is no negligible achievement for the disease is characteristically progressive. Progression may be slow but it is diabolically persistent. These *facts* the patient must understand, as well as his physician, else he feel that therapy has failed utterly, become despondent or angry (depending upon his *personality*), and start "shopping about" for some unscrupulous doctor who promises miracles that cannot be delivered.

In this connection, also, it is better that the patient be made to understand that variations in his arterial tension on different visits are *not* particularly significant, that the precise level of his pressure at a given moment it not important, that it is prognostically more desirable that the tension fluctuate (even to quite high levels) than that it remain fixed because of arteriolarsclerotic changes, that his symptoms, if any, are wholly untrustworthy indices as to how well or sick he is, and lastly, that it is not the hypertension *per se* that the physician is concerned with but the patient who has the disorder. It is desirable to amplify this last concept by pointing out that there exist other facets of health depreciation, such as anemia, obesity, anxiety which affect the hypertension somewhat but affect the patient as an indivisible individual even more. In simplest terms, the objective is to increase the spread between disease-disability-disaster as much as possible.

Logical treatment of hypertensive arterial disease is based upon three fundamental principles. The principles are also applicable to therapy in general. The triad includes: (1) Eradication, wherever possible, of known or suspected etiological factors, (2) rest for the injured structures, and (3) maintenance of adequate tissue nutrition and respiration. Therapy must rest upon a foundation of etiology and all three groups, predisposing, provoking, and perpetuating factors, need to be considered. Frequently, the second principle (rest for the injured structures) overlaps the first. Omission of this consideration permits recurrence and progression of the disease processes, as the changes continue even though the original initiating factors have ceased to exist. Just as with diabetes mellitus, once a hypertensive always a hypertensive, even though the actual elevation of the blood pressure has been erased. If the hypertension was engendered by anxiety, then any recurrence of anxiety can, and very likely will, reinstitute hypertension. The patient has demonstrated his vulnerability; his response to future stresses will follow similar patterns. This applies not only to response to anxiety but also to renal stress (repeated pregnancies, plumbism, or dehydration), anemia, etc. Thus hypertensive patients should be observed periodically even if their pressure has fallen to normal levels. How frequent such observations need to be is determined by the known vulnerability of the individual, the probable or recognized recurrence of the provoking factors, and the duration of the apparent remission.

There are several factors which inevitably limit the effectiveness of any therapeutic approach in hypertensive disease. The lack of symptoms early in the course more often than not contributes to long delay in the institution of therapy; the disorder is usually far advanced when the patient seeks medical aid. Our ignorance of the whole of the etiologic picture is a serious handicap.[53] Hypertension is commonest in later maturity, when the irreversible changes of senescence complicate the problem and make recuperative repair less effective.[1,7,27] The most important factor is the persistent progressiveness of the disorder inherent in its pathogenesis.

Nevertheless, despite these several serious obstacles to fully effective therapy, there is ample justification for an optimistic attitude. Much can be accomplished by intelligent, comprehensive, and individualized manage-

ment. Routinization is ruinous. There is no panacea for hypertension; the immense multiplicity of drugs and methods of treatment sincerely advocated is proof that none is ideal or even generally applicable to all cases of hypertensive disease. As lasting therapeutic results are dependent upon eradication or correction of *all* etiologic factors and as no two instances of the disorder are of identical causation, the absolute necessity of careful, imaginative, extensive etiologic diagnosis and individually tailored therapy should be obvious.

The physician's task is to treat the hypertensive individual, not the disease.

Therapeutic Attack Upon Etiologic Factors: Accurate and comprehensive appraisal of the constellation of etiologic factors applicable to each individual is as yet impossible (for we do not as yet know *all* the potentially provocative factors), but this is no justification for neglecting to search for as many sources of vascular hypertonia as possible Even though the best we may now hope to attain is an approximation of some of the more probable causative factors, this information is crucially important in formulating specific, individualized therapy. It is true that some of the predisposing etiologic factors are irrevocable and not amenable to therapy, but many provoking factors are open to correction. Failure to obtain satisfactory results from treatment in early cases where the hypertension is due solely to arteriolar hypertonia implies continuation of some, perhaps unidentified, provoking etiologic factor.

Early recognition of *potential hypertension* as revealed by an exaggerated rise in response to various stresses (infection, transient intoxications, fatigues, and anxieties) is indicative of individual predisposition. Evidence of such vulnerability may be elicited intentionally by the cold-pressor test[54] or coincidentally during transient illness or stress situations. Temporary fluctuations of the blood pressure upward do not constitute hypertensive disease, but they are significantly indicative of predisposition thereto. It can be assumed that with repetition of the provoking situation the patient will react similarly. Thus one is forewarned of this inherent vulnerability. Prophylactic advice toward avoiding the commoner sources of arteriolar stimulation is indicated.

Such potential hypertension is not infrequently discovered upon examinations which in themselves involve emotional stress. The arterial tension is almost invariably higher when observed in an examination for life insurance than what the patient's own physician finds it to be. A similar emotionally induced rise is frequent in pre-employment examinations or in the annual physical examination required of commissioned military officers In all such instances the examination is "official" and the findings become "a matter of record." Though such exaggerated vasomotor reaction to anxiety does not constitute hypertensive disease *as yet*, the demonstrated vascular vulnerability to such rather mildly threatening situations warrants close attention and a study as to why this patient feels so insecure and anxious [9,17,32,33] Psychotherapy, wisely applied at this point, may prevent the development of irreversible hypertensive disease.[55] Formal psycho-

analysis is rarely indicated. Worry, fatigue, and inexpressible hostility are the particularly pertinent factors which require ventilation.

On the other hand, it is dangerous and careless to assume that a highly fluctuating arterial tension with occasional phases of marked hypertonia, is necessarily of emotional origin. It may well be the earliest evidence of a pheochromocytoma, or chromaffin adrenal tumor.[56] The most important item in the diagnosis of pheochromocytoma is a high index of suspicion leading to test procedures to validate or invalidate the diagnostic impression.[57]

When hypertension develops or is discovered during pregnancy a careful analysis of its pathogenesis is urgently indicated.[58] There are several types of hypertension and/or nephritis which occur in pregnant women.[8,16,35,46] The question of the advisability of future pregnancies is not to be taken lightly. Exacerbations of pre-existing hypertension and/or renal disease by pregnancy are persistent and constitute a true acceleration of the progressive changes rather than merely transient stress response.[59,60]

Other sources of intoxication must be considered and appropriate steps taken to diminish the intoxication. Intoxication with the heavy metals is not uncommon, especially with lead, arsenic, and mercury. Plumbism must be carefully ruled out. Arsenical intoxication from overzealous antiluetic therapy is, of course, much less common than before the advent of modern antibiotic medication. Thyrotoxicosis, often masked and atypical, must always be considered; diabetes and gonadal changes in the climacteric are frequently factors of some importance. It is not necessary to discuss here the therapy directed against these disturbances.

The correction of anemia, which so frequently exists in hypertensive disease, is of the utmost importance As arteriolar constriction impairs the circulation distal to the arterioles (in the capillaries), the quality of the blood becomes increasingly important. It is not exceptional to observe cases of early hypertensive disease respond to antianemic therapy without any other form of treatment. Certainly, in every case, we should strive to raise the hemoglobin content to ninety per cent of optimum and maintain it there.

Focal infections may be important; the majority have existed for a long time. Thorough search for hidden foci of infection is essential; devitalized teeth, chronic tonsillar infection, involvement of the accessory nasal sinuses, and less conspicuous foci, such as pelvic infections, chronic prostatitis, cholecystitis, and urinary infections, must be considered. The prompt and marked improvement which so frequently follows attention to such foci is more than coincidence.

Thorough, intelligent study of the renal functional capacity,[1,16] and diagnostic procedures to discover or rule out unilateral renal disease[41] are indicated in *every* instance of arterial hypertensive disease. The therapeutic results of nephrectomy in cases of unilateral hydro- or pyonephrosis inducing severe hypertension is often dramatic and usually gratifying if performed early enough in the course of the disease.

Therapeutic attack focussed upon correction of etiology must, of necessity, be individualistic. Success is dependent upon the comprehensiveness

of the diagnostic analysis of probable etiology, the amenability of the provoking factors to therapeutic correction, the thoroughness with which *all* factors are attended to and the cooperation of the patient It is fundamental that in the search for etiologic influences (potentially significant even if unproven) the physician is not too readily satisfied by an apparently adequate explanation. Our problem is not to distinguish "this" from "that", but to discover "these and/or those" factors which may be contributing to the genesis of the patient's hypertension. Etiologic factors are not mutually exclusive; they are more likely to be multiple and inclusive The patient with chronic nephritis dating from an infection in youth may very well *also* have a psychic stress, or an intracranial lesion. Thus, it is impossible to generalize in considering these aspects of therapy

However, it is possible to formulate some basic rules of hygiene and diet Moderation or temperance is the gist of wise living. Habits may need some modification but insistence upon extensive and or abrupt alterations in living habits is most unwise. The conscientious patient attempting to follow such advise is often deeply disturbed; others will ignore such recommendations as unfeasible because their habits have been deeply ingrained The physician should not ignore the probability that considerable tolerance may be acquired to such items as coffee, alcohol, tobacco, or irregular hours. Abrupt change may produce withdrawal symptoms, especially in the coffee habitué. Furthermore, real obligations, responsibilities, and life long cultural values and mores must be considered in recommending modifying the *modus vivendi* of adults and particularly older patients.

Exercise can be either beneficial or detrimental to the hypertensive patient depending upon how it is undertaken, its character, the reserve of cardiac competence, and how accustomed the patient has been to the specific type of exertion. It is, of course, highly undesirable and unwise for the obese, flabby, sedentary person abruptly to attempt violent or competitive exercise. On the other hand, to prohibit exercise in the firmly muscled who have kept in training and whose cardiac reserve is not impaired is to invite acceleration of the progression in the hypertensive disease, produce cardiac neuroses, obesity, and premature disablement. Each instance must be individually assessed as to the probable benefits *vs.* the possible detriments, and the character, extent, duration, etc. of exercise prescribed accordingly. Obviously, the soft, obese individual long unaccustomed to exercise must condition himself gradually, for trying to go from subnormal to normal parallels the situation of an athlete training himself to go from normal to superior; gradualness in increasing activity is essential. In general, the benefits derived from exercise (sports) are improved muscular [illegible]

[illegible]

upon the heart in violent effort. It is important that exercise should be [illegible] benefits it must be fun. Those sports or

[illegible]

the like Wisest of all are noncompetitive activities such as swimming,

horseback riding, walking, gardening, fishing. The hypertensive personality is usually so intensely competitive in all life activities that minimal competition in exercise is best.[7]

Tobacco is indicted by some as a major cause of cardiovascular disease, contributing to the genesis of arteriolar hypertension and coronary arteriosclerosis. Statistical data relating the habit of smoking to cardiovascular death rates are highly suggestive of a relationship.[61] But whether this relationship is a simple cause and consequence sequence is by no means proven by the data. Nevertheless such direct causal relationship has been assumed by some and all tobacco smoking vehemently condemned without consideration of many other variable factors.[62] At present the controversy over the evils of tobacco is so beclouded by personal prejudices, emotions, propaganda, and fear in connection with pulmonary carcinoma that *final* appraisal must be deferred. Some physicians go to the extreme of stating that "in the control and treatment of *any type* of heart disease" smoking should be absolutely forbidden. Others have gone to the opposite extreme and ignore the potential role of tobacco in exacerbating hypertensive disease. There is, however, general agreement that smoking is deleterious in arteriosclerosis.[63] However, arteriosclerosis is a different disease and is considered elsewhere in this text. (See Chapter 57).

Extensive studies have revealed that inhalation of tobacco smoke induces vasoconstriction in certain vulnerable individuals.[64] The essential point is that vasopressor sensitivity to tobacco is variable, and therefore either indiscriminate condemnation or approval of smoking is unsound. It is not difficult to individually determine the response of the circulation to tobacco smoke; a few days (eight to fifteen) abstinence and then observation of the pulse rate, arterial tension, and, if deemed desirable, an electrocardiographic tracing before and after smoking will indicate the reactivity of the individual. If the response includes a notable rise in the diastolic tension the objective observation is useful in *convincing the patient* of the undesirability of smoking. We have observed instances of extreme sensitivity (rise of 40 mm. in the diastolic tension and a doubling of the pulse rate to 160) and others in which no change whatever is demonstrable. It must not be forgotten that smoking is a source of desirable mental relaxation, that the majority of smokers are intense, often anxious, driving personalities, and that disruption of any long standing habit produces undesirable additional, and perhaps unnecessary, stress.

Nutritional Measures: *Dietary control* includes a number of significant factors, such as weight control, salt intake, condiments and spices, the use or abuse of alcohol, protein requirements, and the like. Individually these dietary elements vary in therapeutic significance; collectively a wise nutritional regime is of great therapeutic importance. Fads and theories anent diet for hypertensive and renal disease have long affected clinical practice and still do. Even at present there is but one point upon which there is nearly unanimous consensus *moderation.* It must be remembered that the control of hypertensive arterial disease is a long term problem, requiring years of continuous management and that therefore extreme dietary restrictions are as unwise as unlimited excesses. The diet must be directed toward maintaining near optimum nutrition and sufficiently palatable to be

followed. If it be kept in mind constantly that all therapeutic advice is for the *benefit of the patient* who is ill, and not primarily for the treatment of the illness alone, gross errors can be avoided.[1,7,24,65,66] The specific recommendations to be outlined, of course, require individual modification for each patient.

Alcohol, moderately enjoyed is distinctly beneficial by contributing to mental relaxation and encouraging peripheral vasodilation. It is particularly valuable for elderly patients.[65] Abuse to the point of inebriation or depletion of the B group of vitamins obviously is unwise. A few patients need to be warned that "because a little is good, more it not necessarily better."

Coffee and tea are not contraindicated, unless consumed in excess as a means of concealing awareness of fatigue. If thus applied as "whips" by the hyperactive, driving, anxious, intensely ambitious patient their use is best reduced, but not prohibited. A true drug tolerance to caffeine is acquired by coffee and tea addicts and withdrawal phenomena are not uncommon if their consumption is interrupted too abruptly. The withdrawal phenomena are frequently serious (contributing to shock) in addicted patients who are denied all caffeine-containing beverages after a surgical operation. If evening coffee interferes with relaxed sleep, as it will except in habitués with considerable tolerance, it is contraindicated late in the day. In the morning, however, the mental stimulation and the diuretic and the cardiac effects of caffeine are desirable. These beverages, if taken "weak" are often a useful means of increasing the total fluid intake. Caffeine-containing "cola" beverages are far less desirable partly because of their high sugar content and their dental-enamel-destroying acidity.

Condiments and spices are frankly unnecessary dietary constituents. They contribute neither calories, minerals, nor vitamins. Meat extractives (broths, bouillons, gravies, and consommés) are likewise almost nil in food value and are best deleted or reduced to the minimum compatible with a palatable diet. These items are renal and vascular irritants and their abuse etiologically significant.[8] Careful inquiry will reveal that a considerable percentage of hypertensive patients habitually use condiments to excess.

Salt, on the other hand, is a necessary nutritional constituent. It has been known for many years that excesses of salt are deleterious to hypertensive and nephritic patients.[67] It was not until after 1940 that it was realized that the sodium ion was the offending element in table salt.[68] A small minority of patients respond favorably to diets containing no more sodium than 0.2 Gm. per day.[69] The rigid, unpalatable, rice-fruit diet of Kempner[70] has proven significantly useful in only a very small percentage of hypertensive patients.[68,71] In advanced hypertension with renal impairment when extreme reduction of sodium to about 0.2 to 0 3 Gm. per day could be expected to be most useful, no benefit occurs[72] and the danger of the low sodium syndrome is considerable.[73,74] A reasonable regime of restricting salt intake by selecting foods low in salt and adding none in the cooking or at table is palatable and helpful.[75,76]

A liberal fluid consumption is of value; intakes up to six liters (quarts) per day do not raise the blood pressure. Liberal water transport reduces the renal burden, tends to eliminate toxic pressure substances and to re-

duce vascular tonus. Water is probably the best, and certainly the safest, diuretic. It is curious how commonly the question of fluid intake is ignored in nutrition research and in dietary and hygienic advice. In hypertension a consumption of from two to three liters (quarts) per twenty-four hours is to be recommended. Frequently patients are encountered whose ingestion of fluid is far too low; intakes of 0 5 to 1 liter (quart) per twenty-four hours are not unusual. In health the optimum fluid intake should be sufficient to permit of a twenty-four hour urinary volume of 1500 cc. (3 pints). In the presence of renal disease a greater increased fluid intake is of special importance; a low, fixed urinary specific gravity makes a large urinary volume mandatory.[8,16] It matters little how the water is camouflaged; weak tea, fruit juices, milk, carbonated beverages and the like may be suggested for those objecting to drinking unadorned water.

Protein sufficient for normal metabolic requirements is necessary. There is no justification for curtailing protein consumption below the level of 1 Gm. protein per kilogram of body weight usually necessary for remaining in nitrogen balance. Prolonged protein restriction depletes the body reserves, ultimately producing weakness and hypoproteinemia with edema. More immediate is an exacerbation of anemia. As anemia is a not infrequent etiologic factor, protein depletion may aggravate the hypertension without assisting the patient in any other way. Proteinuria *per se* is not an indication for restricting dietary proteins; the continuous daily loss demands a compensatory increase in intake. Hyperazotemia consequent to renal decompensation is another matter; it cannot be considered here. There are no confirmed data supporting the old idea that meats, and particularly "red" meats are deleterious to the hypertensive patient. The source of the protein, animal or vegetable, appears to be wholly immaterial.

Weight reduction is indicated for the obese patients with hypertension; such reduction is usually accompanied by a fall in the arterial tension. Obesity increases the work of an already over-burdened heart, and affects the prognosis adversely, and contributes to the coincidence and severity of complications. It is always possible to effect weight loss without distressing "starvation" by the individualized prescription of appropriate diets.[77] Depending on the degree of obesity, diets of 1200 to 1400 calories daily should suffice. Weight reduction should not be too rapid. In the first place, weakness and the distress of hunger are avoided; secondly, weight lost slowly is much less likely to be regained; and, thirdly, skin and tissue turgor is less affected. The body, apparently, becomes adjusted to gradual consumption of the surplus of stored fat. Shortly the excessive appetite subsides. It is wise to limit reduction to a maximum of 0.9 kg. (2 pounds) per week; 0.45 kg. (1 pound) is better. In this manner, a year's regimen may accomplish a weight reduction of 21.7 kg. (50 pounds) or more without distress or hazard. In many cases the weight loss is associated with a reduction of the blood pressure. And even when this does not occur, reduction in the cardiac load, with lessened dyspnea and fatigue is a significant benefit. Obesity is deleterious in many ways.[78]

Psychotherapy is involved in the proper management of every hypertensive problem. This sweeping statement is justified even in the instances

where the hypertension is clearly secondary to obvious somatic disease (unilateral pyelonephrosis, plumbism, etc.) because hypertensive disease is a chronic disorder where management to control and/or retard progression is a matter of years. It is essential that mutual respect and confidence between the patient and physician be established and maintained in order that cooperation be truly effective.[9] This is not always easy, for many hypertensive patients are bitterly resentful of any implication of impaired health; they feel well and vigorous, are characteristically aggressive and ambitious, and, without awareness of the origin and nature of their hostility, are deeply resentful of the "discovery" of their hypertension (by an insurance examiner, employer-required examination, or other coincidentally consulted physician).[16] They frequently refuse to admit their illness; to do so jeopardizes their invaluable sense of fitness. Others are made intensely apprehensive and are in danger of developing cardiac neuroses unless wisely handled. The sensitive physician is constantly alert to the precariously narrow margin between undue reassuring optimism which can lead to neglect of certain significant aspects of therapy on the one hand, and the danger of inducing iatrogenic exacerbation of the anxiety and therefore the hypertensive disease.[23] An alarmist attitude is usually unwise.

Hypertensive arterial disease, in common with all the other chronic progressive disorders so frequent in the later adult years, requires that *the patient understand* the nature of the disorder if therapy is to be truly effective.[2,3] Here, as with diabetics, arthritics, etc., *effective instruction of the patient* is unquestionably the most important element determining success or failure of any therapeutic regime.[7] The patient lives with himself or herself twenty-four hours a day, every day, seeing the physician but briefly at varying intervals. What happens and how the patient reacts when away from the physician is vastly more important than what the arterial tension is when with the doctor. In chronic illness the doctor-patient relationship must become a teacher-student relationship. After all, originally the term "doctor" meant "teacher." And teaching is a form of psychotherapy: therapy applied to and by the mind.

Clear, simple, and objective explanation of the mechanisms, genesis, causation, effects, and potential menaces (stressing probabilities rather than possibilities) of hypertension can do much to clear the atmosphere of mischief making misinformation, fears, and confusion Interpretation of the *reasons* for each item in the therapeutic program insures effective cooperation. Advice will be followed far more intelligently and conscientiously if the patient knows why it was given, what he may expect to accomplish, and what limitations are inevitable. Advice which is not followed is useless. Phrasing technical information so that it can be comprehended by nontechnically qualified people is an art worthy of intensive cultivation. Unfortunately, it is not deemed deserving of attention in the curricula of modern medical schools and too few physicians are aware of its importance. Recommendation of carefully selected supplemental reading[7] can [illegible] our-aged to [illegible] prob-lems ma[illegible]

In the great majority of cases of arterial hypertension psychogenic factors play some role in the provoking etiology. Their significance and character will, of course, vary in each instance of the disorder. It has been demonstrated that conditioning to restrain, conceal, and/or suppress fears and hostility predisposes to the development of hypertension.[79] Awareness of this predisposing but irreversible factor on the part of both patient and physician is important. Many different studies have revealed that the most common psychic stresses productive of intense and prolonged arteriolar constriction (hypertension) are those related to restraining overt anxiety and especially suppressing intense but inexpressible hostility.[8,9,15-16,17,32,33,80] Clearly it is impossible to elaborate upon the technics, potentialities, and limitations of appropriate psychotherapy here. Rarely is deep psychoanalysis necessary to produce the desired resolution of conflicts, though occasionally the results are dramatic.[17] Relatively superficial exploration of the patient's fears, resentments, frustrations, and particularly suppressed hostilities and their elucidation by a psychiatrically oriented internist or general practitioner can accomplish a great deal without referral to a psychiatrist. Such referral, in itself, can provoke a violent emotional (and therefore vascular) reaction.

Physical Measures: *Baths, massage, diathermy,* and *light therapy* may assist in the general program. Alone, such measures are entirely inadequate; their effect is essentially transient. Baths, massage, and light therapy do assist in obtaining relaxation in selected cases. *Radiation* of the pituitary area with x-rays has been tried but discarded. Massage is particularly useful for patients with cardiac inadequacy; it is vicarious exercise.

Medicinal Measures: Medication in the therapy of hypertension has included almost innumerable substances. The search continues at what appears to be an ever accelerating rate. New synthetic compounds and refinements of natural products, alone or in varying combination, are being introduced at bewildering and alarming pace. Evaluations of effectiveness, limitations, and collateral reactions to these various drugs are frequently hasty, superficial, and inadequate. In this present deluge of enthusiasm for new products of as yet unproven worth the following basic inferences stand out as islands of stability: (1) No specific drug has been found which will produce uniformly satisfactory results; (2) it is not probable that one such will be found, for hypertensive disease is individually highly variable, each case being unique; (3) the auxiliary use of drugs for specific objectives is of value, but medication alone does not suffice, curative therapy is dependent upon amelioration of the etiology; (4) there is urgent need for critical inquiry into *why, when, where,* and *for what* we use these new weapons in contrast to study devoted to *how* to create and apply them. Technics have received far more attention than objectives and purpose.

The administration of pharmacologically active medication in hypertensive disease can (1) serve as a sedative, contributing both to better sleep and rest as well as reducing the emotional turbulence during waking hours, (2) act as vasodilators, either by direct action upon the arterioles

or through interfering with neurogenic stimulation, (3) contribute to the general well-being through adjusting metabolic and hormonal equilibrium, (4) assist in maintaining functional competence of the two vital organs most commonly injured in hypertensive disease, the heart and the kidneys.

Sedatives in small amounts over a long period of time assist in the attainment of relaxation. For some years the most satisfactory sedative drugs were the barbiturates, although they become less and less effectual with prolonged use. Furthermore, phenobarbital is definitely depressant; it has an almost specific effect of lowering morale. The barbiturates are poorly tolerated by the elderly.[1] Recent studies suggest that *dilantin sodium* 30 mg. (½ grain), three times per day, may be most helpful in anxiety states.[81] Frequently patients report that their work and intellectual efficiency is improved by such mild selective sedation. Alcohol, judiciously consumed, can be an excellent relaxant. The bromides, formerly very popular, are justifiably falling into disrepute. Bromide salts are too readily available for self-medication so that amounts in excess of those recommended are consumed without the physician being aware of this habit. Bromides tend to accumulate, particularly if there is any renal functional impairment. Bromidism is most insidious. Bromural (monobromisovalerylcarbamide), despite its name is not a bromide, nor is it a barbiturate.

Within the last two or three years there have been developed a number of nonbarbiturate, mild, so-called "mood changing" sedatives. These include dormison, doriden, miltown, equanil, and several more. Their effectiveness in hypertensive disease is as yet undetermined. More potent is chlorpromazine hydrochloride (known more commonly in the United States as thorazine) which has proven extremely valuable for acutely agitated psychotic patients.[82] It is known to cause a moderate reduction of blood pressure,[83] but it is too toxic to hazard many months of administration in ambulatory patients.[82-84] It has been reported[85] that when used in combination with rauwolfia serpentina the effectiveness of the latter is enhanced.

The most useful and the safest nocturnal sedative is chloral hydrate, now available in both a palatable elixir and capsule form.

Vasodilator drugs are now available which are not only adequately effective but also whose effects are sufficiently prolonged to be truly helpful. The highly soluble *nitrites, amyl nitrite, sodium nitrate, mannitolhexanitrate,* and *erythroltetranitrate,* etc., are too transient in their action to be of v

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the co

logue of papaverine), nitroglyn (coated delayed action nitroglycerol), and peritrate (pentaerythroltetranitrate). A comparison of these three concludes[86] that peritrate appears to satisfy the need for prolonged (five to six hours) coronary vasodilation in most patients with angina pectoris. It is also useful in hypertension *per se.* The effectiveness of peritrate in reducing the arterial tension and in increasing the cardiac reserve for effort

is similar to the responses to bismuth subnitrate first reported over twenty-five years ago.[87]

Potassium sulfocyanate produces some prolonged arterial relaxation, but it is not entirely without harm; many reports of extensive intoxication have appeared. The commoner manifestations of thiocyanate intoxication are muscular weakness, dermatitis, nausea, vomiting, mental confusion and disorientation, aphasia, convulsions, and terminal coma. The general consensus is that the sulfocyanates in effective amounts are too dangerous unless the patient is under close control. Safer and more effective drugs are now available.

Hexamethonium chloride, available under several different trade names, is an effective autonomic ganglionic blocking agent and capable of reducing high blood pressure.[88] In one considerable series of hypertensive patients sixty-four per cent of the cases were well controlled for a year or more with hexamethonium as the only therapeutic agent. It is effective in late severe malignant hypertension[89,90] but its administration requires extremely close supervision. The vasodilating response does not remain uniform; postural hypotension, syncope, blurring of vision, and stubborn obstipation are objectionable side effects. Smaller doses in combination with 1-hydrazinophthalazine (hydralazine) have been tried with apparently some benefit though the period of observation of many of the patients was too short to warrant any general conclusions.[91] Hydralazine (trade name apresoline) is a rapidly acting vigorous vasodilator. It is too toxic for general use in hypertensive disease, though some modern clinical investigators seem to be so charmed by the immediate dramatic results that they ignore late systemic complications. The late reactions include fever, pancytopenia, acute psychoses, gastrointestinal bleeding, and a collagen-like illness resembling acute rheumatoid arthritis or simulating acute systemic lupus erythematosus.[92] Such hazards do not warrant the application of the drug in a disorder so slowly progressive as hypertensive disease.

Veratrum viride has long been employed empirically in the treatment of eclampsia. Recent identification of several alkaloids isolated from the crude drug revived interest in the hypotensive effect of these substances It is reported that the margin between toxic and hypotensive doses is not appreciably greater with the pure alkaloids than with the crude drug Although good control over the blood pressure can be obtained, the toxicity prevents continuing therapy over a long enough period of time.[93] Oral administration of veriloid, a standardized mixture of hypotensive alkaloids, to hospitalized patients with malignant hypertension appears to be useful; there is no rationale to using veriloid in the treatment of ambulatory benign hypertension.[94]

Pentolinium tartrate (ansolysen) is another addition to our armamentarium of hypotensive agents. It is reported as being five times more active than hexamethonium in producing sympathetic ganglionic blockade, and its duration of action is much more prolonged.[95] It has been recommended for severe and malignant hypertension, but not for mild, labile spastic hypertension. Until recently no serious complications have been reported, but any potent hypotensive agent may, by inducing relative hypotension,[8] cause cerebral or coronary thrombosis and occlusion.[96]

Rauwolfia serpentina, derived from the root of a shrub indigenous to India, and used for centuries for many ailments including manic mental states, is perhaps the most satisfactory of all the new hypertensive drugs. The crude drug contains several alkaloids. The therapeutic results are not notably different whether whole root or isolated alkaloids are employed, though there is, of course, considerable difference in potency.[97] Studies indicate that 1 mg. of pure reserpine is equivalent in hypotensive activity to 250 mg. of the crude root.[98] The usual oral dose is from 50 to 100 mg. rauwolfia serpentina or 0.25 to 0.5 mg. reserpine two to three times daily.[99] In most instances a gradual and fairly well sustained reduction in arterial tension results.[100] The drug is thought to act directly upon the autonomic centers of the brain stem, probably by suppressing higher sympathetic centers in the hypothalamus.[101] Side effects are nasal and conjunctival congestion, increased anxiety, excitement, and vertigo. With overdosage depression, nausea, vomiting, and diarrhea may be encountered.[102] None of these is serious, except the occasional occurrence of severe depressive reactions.[103,104,105]

There have been many attempts to evaluate not only the relative usefulness of these new drugs[107,108,109] but also the effectiveness of combinations of two or more compounds.[110,111] None of these studies comes to any definitive conclusion. Hypertensive arterial disease progresses at such variable rates in different patients,[112,113] is often so benign as to require no medicinal therapy,[114] and is so responsive to attention to the emotional problems,[115] and confidence in the physician[116] that accurate appraisal is truly impossible. It will require years of observation before these questions can be answered, for short term improvement is not necessarily followed by long term gain In general, the milder and less toxic the vasodilating agent employed and the more persistent its action, the better are the long term results and the fewer are the undesirable complications.[8,16,50,117]

Surgical Measures: Surgery contributes to the treatment of hypertensive disease in several ways. Unilateral nephrectomy in clearcut instances of unilateral renal disease can be dramatically effective in arresting this progressive disorder, but the indications must be well defined and good renal function of the remaining kidney demonstrated before it is justified. Removal of pheochromocytomata, may be life-saving.[118] But these two etiologic pictures account for only a very few instances of hypertension.

In the last decade, neurosurgical attack has made immense progress. Extensive thoracolumbar sympathectomy induces a great reduction of the arterial tension through paralysis of the vasotonic nerves of the splanchnic and visceral areas.[119] Several operations have been devised.[120,121,122] The technic of Smithwick[123,124] is now favored, though there is no general agreement as to which is the most effective and least hazardous.[125] The results, if measured in terms of reduction of the arterial tension, are said to be very good,[126] but as often tabulated are somewhat misleading inasmuch as there appears to be a diminishing return of favorable results the longer the patients are followed.[127] The most logical method of evaluating ... arding the reduction of tension in mm. Hg, but in per-

centage approach toward normal, and the duration of the improvement.[16,50,128]

Among the disadvantages of sympathectomy, other than considerable immediate surgical hazard, are orthostatic tachycardia, coldness of the extremities, syncope, and breathlessness. With splanchnic vasomotor paralysis, excessive compensatory vasoconstriction in the extremities may induce the phenomena of Raynaud's disease. The advisability of this surgical approach depends upon a number of factors; certainly more conservative medical management should be given careful trial and every effort made to discover the specific etiologic pattern so that therapy can be directed to correction of the etiology. Even in malignant hypertension, the newer potent ganglionic agents give some promise that surgical sympathectomies will become obsolete,[129] and that the even more radical subtotal adrenalectomy alone and/or combined with sympathectomy[130] will likewise be outmoded.

SUMMARY

It cannot be overemphasized that the most important characteristics of hypertensive arterial disease are the tendency to persistent progression and the cumulative and multiple etiologic influences. No two instances of the disorder are necessarily alike in their causation. Every case is an individual problem. Routinization in therapy is to be avoided; the greater the diagnostic thoroughness in searching for etiologic factors, the better will be the therapeutic results. Individualization is essential; each patient with hypertensive disease should be viewed as a problem of clinical research.

Comprehension of the pathogenesis and the pathologic physiology consequent to hypertension is essential to intelligent management. The fundamental consequences of arteriolar constriction are dual and ambivalent: *proximal* to the arteriolar constriction the intra-arterial pressure rises with the increased peripheral resistance against the cardiac force and *distal* to the arteriolar constriction a diminished blood flow, capillary ischemia due to hypotension.[8] It is the latter consequence of tissue histanoxia which leads to much of the insidious parenchymal, cerebral, renal, and myocardial injury.[131] This aspect warrants more consideration than it has received heretofore.

As effective therapy must be based upon a knowledge of causation, a truly useful diagnosis in hypertensive disease includes consideration of: (1) The probable etiologic factors, (2) the stage of pathogenesis, (3) the degree of functional impairment of the heart, kidneys, and the like as consequences of hypertensive histanoxia, and (4) evaluation of complicating coincident disorders. In considering etiology, it must not be forgotten that the predisposing factors can be just as significant as provoking or perpetuating influences. To neglect even one apparently insignificant provoking or perpetuating etiologic factor is to jeopardize the effectiveness of conservative physiologic management. We must focus our attention upon the patient, rather than treat the disease, to obtain the best results. The individual is indivisible.

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28

The Cardiovascular System with Relation to the Kidneys

Introduction: While the function of every organ in the body is dependent on an adequate blood supply, the relation between the cardiovascular system and the kidneys is particularly intimate. Bier expressed this in saying, "The heart and kidneys together secrete the urine." The relation is a reciprocal one. Inefficiency of the heart, with diminished blood flow or inadequate blood pressure leads not only to a decreased urinary output, but to the appearance of abnormal constituents such as albumin in the urine. Primary kidney disease of certain types on the other hand leads to an elevation in blood pressure and all the train of events in the cardiovascular system included under the term "hypertensive heart disease."

While the processes involved in the formation of urine in the kidney are extremely complex, physiologists are now pretty generally agreed on the fundamental importance of three mechanisms, glomerular filtration, tubular reabsorption and tubular secretion. As blood flows through the glomerular capillaries, there is separated from it, by a purely physical process, an almost protein free ultrafiltrate of plasma, containing all the dissolved substances present in plasma Except for minor differences in the concentration of certain electrolytes due to the impermeability of the normal glomerular membrane to protein, and which is spoken of as the "Donnan effect," these dissolved substances are present in the glomerular filtrate in the same concentration at which they exist in plasma. As this glomerular filtrate passes down the renal tubule, it is modified by the active reabsorption of water, glucose, sodium, chloride, etc , by the tubule cells and the diffusion of a certain amount of waste products, such as urea, which have been concentrated in the lumen of the tubule by the reabsorption of water, back from tubular lumen into peritubular capillaries. In addition to these two processes of glomerular filtration and tubular reabsorption, there is convincing evidence that at least certain substances are transferred from the peritubular capillaries to the lumen of the tubule by secretion.[1]

Of naturally occurring substances in man, creatinine, potassium, hydrogen ion hippuric acid and ammonia are so handled in part by secretion. Several exogenous substances which are used as tests of kidney function,

such as phenolsulponphthalein, diodrast and para-aminohippurate are secreted. Further, Pitts and his associates have presented convincing evidence that the amount of titratable acid excreted in the urine cannot be accounted for by the amounts of phosphate and carbonic acid filtered. It seems that acid must be added to the filtrate as it passes along the nephron, and that this addition of acid is apparently affected by the exchange of hydrogen ions formed within the tubular cells for cations in the tubular lumen.[1a]

In order that there may be filtration in the glomeruli, there must first of all be an adequate blood pressure in the glomerular capillaries to overcome the osmotic pressure of the plasma proteins and to drive the filtrate through the tubule. In the frog, glomerular capillary pressure averaged fifty-four per cent of systolic aortic pressure;[2] in the isolated perfused mammalian kidney Winton[3] estimated the glomerular pressure as two-thirds of the mean aortic pressure. Applying these experimental results to man would indicate that with a mean aortic pressure of 110 mm. Hg glomerular capillary pressure would be about 60 or 70 mm. Hg. The colloid osmotic pressure in man averages about 25 mm. Hg, leaving a filtration pressure of 35 or 45 mm. Hg. Urine formation must of necessity stop when systolic aortic pressure falls to 50 mm. Hg; as a matter of fact, however, it usually ceases when systolic pressure has fallen to about 75 mm. Hg, or even higher figures in patients with hypertension and marked sclerosis of the smaller renal arterioles. Systolic blood pressures of 75 to 80 are not infrequently encountered in severe coronary occlusion as well as in surgical shock and Addison's disease. It is obvious that under such circumstances little or no excretion of urine will occur, and that attempts to produce diuresis by drugs which act on the kidney are bound to fail. Attention must be directed toward improvement of the circulation and elevation of blood pressure. If this is accomplished, urine excretion will take care of itself. When these low blood pressures have lasted for some hours or days there will, of course, be retention of waste products in the body with elevation of blood urea nitrogen, etc.

It was stated above that the normal glomerular membrane is impermeable to the plasma proteins, and that the glomerular filtrate is almost protein free. While this is the generally accepted view, there are some workers who believe that the glomerular filtrate normally contains 10 to 20 mg. per cent protein which is reabsorbed by the tubular epithelium. According to this view, while in clinical albuminuria there may be an increased leakage of protein through the glomeruli, the essential fault is failure or saturation of tubular reabsorptive capacity.[3a] If, however, blood flow and consequently oxygen supply to a glomerulus is reduced, the permeability of the membrane is increased so that it leaks protein. Hermann[4] demonstrated years ago (1862) that transient albuminuria followed temporary compression of the renal artery. Subsequent work has shown that the glomerulus is the structure in which the escape of protein in this condition takes place. Starr[5] showed that transient albuminuria followed renal vasoconstriction produced by a variety of means such as infusion of adrenalin, inhalation of CO_2, ephedrin or fright. These observations were explained by the conception

that renal vasoconstriction causes increase in the duration and extent of the normal intermittent interruptions in the glomerular circulation. Permeability of the glomerular membranes is so increased by these lengthened interruptions that when blood flow is reestablished albumin escapes. This conception may apply to those albuminurias in man which result from severe muscular exercise or from emotion or which are produced reflexly. It may explain the occurrence of albuminuria in the urine of normal people.

CONGESTIVE HEART FAILURE

The most marked albuminurias from partial asphyxia of the glomerular membrane probably occur in congestive heart failure. Here there is an increase in venous pressure and a diminished cardiac output, both of which decrease the rate and volume of blood flowing through the kidneys. The urine output in congestive heart failure is usually reduced in proportion to the degree of failure. The specific gravity is high, and the urine contains a considerable amount of protein, hyaline and granular casts, and not infrequently an abnormal number of red blood cells. Kidney function, as measured by the excretion of phenolsulfonphthalein or clearance tests, is reduced. When the urine volume is reduced to a point where, for a given specific gravity, it is too small to contain all the waste that must be eliminated per day, nitrogen, as urea and creatinine, and other substances, accumulate in the blood. The relation of renal blood flow to cardiac output in congestive failure has been the subject of several studies. While some data indicate that the renal blood flow is reduced in proportion to cardiac output,[5a] more support the belief that the renal blood flow is disproportionately reduced,[5b] and that this disparity is still more marked during exercise.[5c] Since the reabsorption of sodium from the glomerular filtrate is remarkably constant, some 13.3 from every 100 cc. of glomerular filtrate, the reduction in renal blood flow and glomerular filtrate results in retention of sodium and edema.[5d]

The degree of nitrogen retention may be surprisingly great, figures that are usually considered indicative of uremia being not infrequently encountered. However, nonprotein nitrogen values above 100 usually are indicative of some pre-existing kidney disease or a purely renal complication. All these evidences of kidney disease improve or disappear with the restoration of cardiac compensation. These abnormal findings should not be taken as justifying a diagnosis of "cardiorenal disease" They are simply the result of inadequate renal blood flow. Of course a patient may have organic kidney disease, either glomerulonephritis or nephrosclerosis in addition to cardiac failure. But I know of no way to estimate the degree of such pre-existing kidney insufficiency in the presence of cardiac failure. Such studies must wait until compensation has been restored. A concentration test performed while a patient is losing edema, for instance, is meaningless.

It is in the edema of heart failure, with normal or relatively normal kidneys, that diuretics are most effective[6] But all of them are more effective after the patient has been digitalized than before. Digitalis itself,

for marked fluctuation in blood pressure than there is in early essential hypertension. The hypertension results in hypertrophy of the left ventricle, but this is often relatively slight, and the heart may be able to cope with the increased work for years without dilatation.

While slight dyspnea on exertion is not unusual, severe degrees of cardiac failure are uncommon, the chief danger always being the progressive renal insufficiency. There are, however, some long-standing, slowly progressive, cases of chronic glomerulonephritis in which the clinical picture of cardiac insufficiency develops. With the long-continued hypertension, the left ventricle gradually fails. Following this a train of symptoms, including dyspnea, cardiac asthma, gallop rhythm, and attacks of pulmonary edema, make their appearance. Arterial symptoms, such as angina pectoris, cerebral angiospasm, and spasms of peripheral vessels, which are so common in primary hypertension, are unusual.

Cerebral hemorrhage is also distinctly uncommon in glomerulonephritis, since this disease usually occurs in relatively younger individuals whose cerebral arteries are rarely atheromatous. When weakness of the right heart also develops, engorgement of the liver, peripheral edema, and all the other evidences of congestive heart failure appear. It is to be emphasized that while such a patient has chronic glomerulonephritis, that under these circumstances the edema is cardiac, and not "nephritic," and that the treatment should be that ordinarily employed in congestive failure. Feil and Steuer[16] found that digitalis was just as effective in the presence of nephritis, and that the dosage was the same as in the non-nephritic. It must again be emphasized that marked cardiac insufficiency in the preuremic stages of glomerulonephritis is not common. While dyspnea may be troublesome, both the acidosis resulting from the retention of fixed acids and the anemia contribute to this.

As a rule, with the development of symptoms of true uremia, signs of cardiac insufficiency frequently make their appearance. It might be thought that the cardiac weakness was primary, the diminished blood flow leading to oliguria, which prevents the maintenance of the compensatory polyuria, and that consequently retention develops and uremia supervenes. This conception, however, is not consonant with the clinical observation that unmistakable signs of fatal uremia, as uncontrollable vomiting, pericarditis, and marked nitrogen retention, may come on without any significant decrease in urine volume. There is no doubt, however, that the association of cardiac insufficiency and deepening uremia is not coincidental. For in every case, urine volume, dependent on the renal circulation, is relatively reduced; that is, it is inadequate for the elimination of waste at the low concentration which can be attained in the damaged kidney.

On the other hand, in every case the heart may be considered to be inadequate to meet the demand for increased blood flow imposed by the loss of concentrating ability by the kidney. It seems that some retained waste product, or other change in the composition of the blood in uremia exerts a directly deleterious effect on the heart. This is undoubtedly due to potassium retention and to changes in the potassium: calcium ratio in

the plasma. Thus Wood and White[17] found changes in the electrocardiogram which varied from day to day. Extrasystoles, transient auricular fibrillation, and pulsus alternans are common. The uremic pericarditis was first noticed by Bright. Its etiology has been much discussed, and while some have thought it infectious, the exudate is usually sterile, and it would seem that it is most often, if not always, a sterile inflammation due to some substance retained in the blood as a result of kidney insufficiency.

ESSENTIAL HYPERTENSION

The symptoms, clinical picture and treatment of this condition are discussed elsewhere. In this chapter we are concerned only with the relation of the kidneys to the elevated blood pressure of essential hypertension that is evidence for the renal origin of "essential" hypertension. As Volhard has remarked, the problem is a beloved but annoying child of internal medicine.

More than 100 years ago, before blood pressure had been determined in man, Bright[18] observed the frequent coexistence of cardiac enlargement, thickening of the arteries, and renal disease of various kinds. Finding no obvious cause for the cardiac hypertrophy in the heart or great vessels, he attributed it to an effect produced by an altered state of the blood which he felt convinced was caused by the renal disease. He may thus be regarded as the first to postulate the renal origin of hypertension. Traube[19] was the first to express a definite view of the relation between kidney disease and hypertension, but regarded the latter as the direct result of the increased resistance offered by the narrowed renal vessels. This view has no physiological basis, and has been abandoned by all except those addicted to teleological explanations.

Gull and Sutton[20] confirmed Johnson's[21] demonstration of lesions in the small vessels of other organs than the kidney. Impressed by the widespread nature of the process, which they called "arteriocapillary fibrosis," they concluded that diffuse vascular disease was a pathologic entity and could be responsible for an increase in arterial pressure. Gull and Sutton thus founded a school which stressed the nonrenal origin of hypertension, and has had numerous followers to the present time.

With the introduction of the sphygmomanometer into clinical medicine by von Basch, attempts were naturally made to correlate elevation of blood pressure with changes in the blood vessels. But many cases were found which showed definite elevation in blood pressure, in which arteriosclerotic changes were either absent or minimal. These cases von Basch[22] called "latent arteriosclerosis" Huchard[23] in France, Allbutt[24] in England, and Janeway[25] in this country, believing that the organic disease of the arterioles was not sufficient to produce enough increase in peripheral resistance to account for the observed elevations in blood pressure, suggested that this was due to widespread vasoconstriction. According to this hypothesis, functional vasoconstriction was primary, organic vascular arteriosclerotic changes secondary.

"Up to the turn of the century, there were three schools of thought concerning the interrelation of hypertension, arteriosclerosis and renal dis-

ease: (1) The followers of Bright, who believed that hypertension was due primarily to renal disease; (2) the followers of Gull and Sutton, who ascribed hypertension to widespread vascular disease and regarded the renal lesions as purely secondary; and (3) those who believed with Allbutt that hypertension was due to generalized vasoconstriction unrelated to renal disease."[26]

With the separation of contracted kidneys into two groups, an inflammatory and an arteriosclerotic by Jores[27] and by Volhard and Fahr,[28] a distinct advance was made. It was now generally accepted that hypertension was the result of primary renal disease in glomerulonephritis, polycystic kidneys, obstruction of the urinary passages, and renal panarteritis. In the other, and numerically larger, group of patients who showed hypertension during life and only arteriosclerotic changes in the kidneys at autopsy, the hypertension was usually regarded as not of renal origin.

The vast majority of patients with essential hypertension show more or less vascular disease which is frequently more marked in the kidneys than elsewhere. For example, Bell and Clawson[29] found renal arterial disease in ninety-eight per cent of 420 cases of hypertension, and Fishberg found some change in each of seventy-two cases studied. Only Moritz and Oldt,[30] among recent workers, have attributed particular significance to the renal lesion. In a careful objective study of arteriosclerotic changes in the vessels of the viscera and muscles from 100 patients with hypertension and 100 with normal blood pressures, they found a high degree of correlation between the presence of renal vascular disease and hypertension, and no such correlation between arteriosclerosis elsewhere and hypertension.

The whole aspect of the problem was changed, and the relation of kidney disease to hypertension greatly clarified by the investigation of Goldblatt[31] and his associates.

When a clamp was applied to one of the main renal arteries, which diminished renal blood flow as would occur in arteriolar sclerosis, in either dogs or monkeys and moderately tightened, there followed in the course of the next couple days a rise in blood pressure of around 50 mm. Hg. This, however, usually fell toward or to normal in the course of weeks or months. When both renal arteries were constricted the hypertension persisted indefinitely. Goldblatt had such dogs, with systolic blood pressures of 200 to 240 under observation for more than five years. These animals, furthermore, in spite of their elevated blood pressure, did not show any decrease in kidney function as measured by urea or creatinine clearance tests or concentrating ability or elevated blood nitrogen. If in such an animal, with persistent hypertension, Goldblatt loosened the clamps on the renal arteries, the blood pressure promptly fell to normal. Constriction of other arteries, femorals, splenic, or splanchnic did not produce any elevation in blood pressure. These results have been confirmed by many other investigators.

If the degree of constriction of the renal arteries is made extreme, Goldblatt found that the animals not only develop renal insufficiency and die in uremia, but that in some there develops widespread fibrinoid and hyaline degeneration, with necrosis of arterioles, petechiae in intestinal tract,

serous membranes and many organs, but not in the ischemic kidneys. These lesions are similar in all respects to those observed in the acute malignant phase of essential hypertension in man (Fig. 3).

Pathogenesis: The pathogenesis of this experimental hypertension has already been the object of a great amount of study. It seems obvious that the increase in blood pressure must be brought about by a general increase in peripheral resistance, just as it is assumed in human essential hypertension.

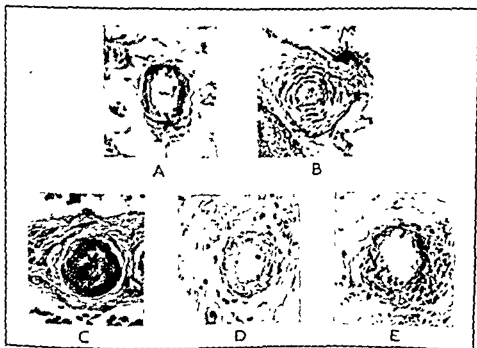


FIGURE 3 Photomicrographs of arterioles from dogs with experimental hypertension due to renal ischemia Kindness of Dr Goldblatt All sections X232, hematoxylin and eosin stain *A*, Normal arteriole, skeletal muscle *B*, Arteriole of skeletal muscle, with hypertrophic media Dog hypertensive four years, no detectable renal excretory insufficiency (benign phase), due to moderate constriction of both main renal arteries *C*, Hyalinized, obliterated arteriole. From submucosa of stomach of dog with marked hypertension and acute renal insufficiency (malignant phase), due to excessive constriction of both main renal arteries. *D*, Necrotic arteriole Submucosa of intestine of hypertensive dog in the acute malignant phase *E*, Necrotizing arteriolitis Submucosa of intestine, hypertensive dog in the acute malignant phase

Neglecting the teleological explanation of a purposeful elevation in pressure to improve renal blood flow, only two mechanisms suggest themselves, either a nervous reflex from the ischemic kidneys which affects the general vasomotor apparatus, or a humoral mechanism "initiated by the ischemic kidneys due to the formation or accumulation in the blood of a substance which, directly or indirectly, constricts the peripheral vessels. The possibility that such a substance might act on capillaries or by neutralizing a natural depressor substance must also be mentioned."[31a]

Many experiments from Goldblatt's group and from others have failed to show that a nervous mechanism has anything to do with this type of experimental hypertension. Thus denervation of the renal pedicle, section of the splanchnic nerves and excision of the lower four thoracic sympathetic ganglia, section of the anterior nerve roots from the sixth dorsal to the second lumbar, and even excision of the entire sympathetic nervous system in the thorax and abdomen, or pithing, have failed to prevent or to cure the hypertension. On the other hand, if one kidney is removed and the other transplanted to the neck, so that there can be no possible direct connection between kidney and nervous system, elevated blood pressure develops when its artery is constricted.[32] Thus, a humoral mechanism is left as the only probable mechanism.

At the end of the last century Tigerstedt and Bergmann[33] obtained a rise in blood pressure in anesthetized animals by injection of saline extracts of normal kidneys, and actually suggested that there might be an increase in this pressor substance, which they called *rennin* in the kidneys of hypertensives. Some investigators confirmed Tigerstedt and Bergmann, others did not, while Collip[34] obtained a "nonspecific" pressor principle from a variety of tissues. Goldblatt's work has naturally stimulated renewed interest in such experiments.

Landis[35] and his collaborators have prepared an extract of normal kidneys which elevates blood pressure without diminishing skin temperature or reducing the amplitude of arterial pulsation. Harrison and his co-workers,[36] and Prinzmetal and Friedman,[37] reported a larger amount of pressor substance in extracts of ischemic kidneys of experimental hypertension and arteriosclerotic human kidneys than in similar extracts from normal kidneys. Fasciolo, Houssay, and Taquini[38] have reported that when an ischemic kidney from a dog whose renal arteries had been compressed for from three to forty days is transplanted into the neck of an anesthetized nephrectomized animal, and the necessary vascular anastomosis completed with carotid artery and jugular vein, the blood pressure of this animal promptly rose 30 to 70 mm. Hg, and then remained stable at this figure or slightly lower. Moreover, the transplanted kidney could be removed and placed in the neck of still another animal which in turn showed a rise in blood pressure.

A serious obstacle to acceptance of the renal origin of human hypertension was the failure to demonstrate hypertension in the blood of patients with either benign or malignant hypertension. Using improved methods Skeggs, Kahn, and Shumway[38a] were able to isolate hypertension first from dogs with constricted renal arteries, and then from normal animals.[38b] Later they demonstrated small amounts in the arterial blood of some normal persons, slightly more in some patients with benign hypertension, and considerably more from those in the malignant phase.[38c] They have recently shown that this substance is a polypeptide containing about nine amino acids, and is about four times as powerful a vasoconstrictor as l-arterenol.[38d] This work has furnished important support for the theory of the renal origin of many cases of hypertension.

The similarities between human essential and experimental renal hyper-

tension have been well summarized by Goldblatt.[31a] Although Goldring and Chasis[38c] concluded that the weight of evidence is against the identity of the mechanism in human and experimental renal hypertension yet it has been shown by many investigators that the experimental procedure reproduces the human disease in many respects. In both, the increased tension is the result of a generalized increase of peripheral vascular resistance of functional origin. In experimental renal hypertension, as in human hypertension, there may be no significant disturbance of renal excretory function (the benign phase) or there may be pronounced renal excretory functional disturbance, with uremia (the malignant phase). In both cardiac action is increased, but cardiac rate, output, volume, viscosity, and peripheral blood flow and venous pressure are unaltered. Renal blood flow is reduced in most cases of human hypertension as well as in the animals. The indirect studies of blood flow through the kidneys in man do not reflect the sclerosis of the afferent arterioles, because the vasospasm of efferent vessels results in a high glomerular filtrate fraction which tends to mask it. In the benign phase of hypertension, in both man and animals, cardiac hypertrophy develops, and medial hypertrophy of the arteries. In both humans and experimental animals, the level of blood pressure tends to be higher in animals that gain weight.

The primary role of renal ischemia in the production of essential hypertension is by no means universally accepted however, Thomas[7e] has reemployed the relation of heredity and body build to the development of hypertension. Some psychiatrists maintain that persons with essential hypertension are characterized by repressed aggressiveness, while others believe that they are similar to normotensive persons as far as adjustments to emotional problems are concerned Attempts at psychiatric treatment usually fail to lower blood pressure although the patient may feel much better if his problems are resolved. Other possible mechanisms and points of view are summarized by Wakerlin.[3f]

One very interesting practical application of Goldblatt's work has been the discovery in children and adults of hypertension associated with unilateral pyelonephritis and vascular disease and the prompt return of the blood pressure to normal after removal of the diseased kidney. Such cases have been reported by Butler,[39] Barker and Walters,[40] and others.

Just as Goldblatt's dogs showed persistent elevation in both systolic and [illegible] the [illegible] sign[illegible] less than ten per cent of these patients die in uremia, or present evidence of renal insufficiency before death. The great majority succumb to cardiac failure, cerebral hemorrhage or intercurrent infection. In most of these patients, tests of kidney function, either the concentration test or urea clearance, are within normal limits. At times there will be a low excretion of phenolsulfonphthalein with a normal concentrating ability, but this is more properly related to cardiac weakness than to renal impairment. The urine in this group is of normal volume, does not contain an abnormal number of red cells, and frequently no albumin. Other patients may show

a slight transitory albuminuria, often related to periods of cardiac weakness, while still others excrete a small amount, less than a gram a day, of protein constantly.

The logical method of treating these patients would be to attempt to improve their renal blood flow. At present direct methods for such an approach have not yet been developed. Quite possibly the benefit that is not infrequently seen to follow periods of rest and relief of nervous and emotional strain in patients with essential hypertension is the result of improvement in the renal circulation, for the kidneys are richly supplied by vasomotor nerves.

The great number of remedies which have been recommended for the treatment of hypertension indicates that none is of particular value. The use of salt-poor diets has been revived, particularly by Kempner[40a] who combines salt restriction with a low protein diet composed of rice, sugar, and fruit juices. Opinions in regard to the effectiveness of this diet have varied from brilliant to insignificant. Whatever moderate fall in blood pressure occurs is probably due to the low sodium content rather than to low protein or any other specific character of the diet. Even the rationale of sodium restriction is far from clear. Its proponents adhere to the thesis that the adrenal cortex is somehow involved in the genesis of the elevated blood pressure which leads to a disturbance of sodium metabolism and a high sodium-to-chloride ratio While some reports indicate a significant reduction in blood pressure with sodium restriction, the majority of physicians have been decidedly disappointed.[40b]

The rationale of sympathectomy for hypertension rests on the belief that it begins as a functional vasoconstrictive disease mediated through the sympathetic nervous system. After observations on several thousand patients, opinions vary from insignificant to brilliant results. Some hold that the ideal patient is the early labile hypertensive, others that the operation should be reserved for those with advanced vascular disease. Some stress relief of symptoms rather than any lowering of blood pressure. However, occasional brilliant results are achieved. Unfortunately these individuals cannot be recognized in advance of operation. Fishberg,[40c] from his own experience, believes that sympathectomy is indicated in less than four per cent of patients with essential hypertension. The general management of essential hypertension is discussed elsewhere in this volume.

A smaller group of patients with essential hypertension do show moderate impairment of kidney function. This is related to the number of glomeruli destroyed by the arteriosclerotic process.[41] Such patients, after several or many years of hypertension, may be unable to concentrate their urine above 1.015 and have urea clearances of forty to fifty per cent of the normal. They excrete a moderately increased volume of urine, and often have some nocturia. By virtue of this "compensatory" polyuria, they are spared any retention of nitrogen in the blood, nor do they develop any anemia, which is so constantly found in chronic glomerulonephritis. Although the destruction of glomeruli in the kidney by the arteriosclerotic process is progressive, it is usually so slow that the patient dies of cardiac failure or some other cause before the kidney mass has been reduced to a

point which precipitates uremia. The number of glomeruli remaining in a kidney does not bear any relation to the reduction in its weight, since the amount of scar tissue, pelvic fat, etc., differs tremendously in different individuals.[42]

Finally, there is a small group of patients, usually in the sixth or seventh decade of life, who have had hypertension for many years, and who, we may suppose, have unusually good hearts, who develop kidney insufficiency and die in uremia. Counts of the number of glomeruli in such kidneys at

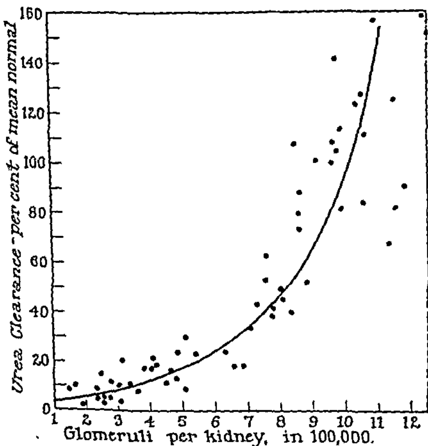


FIGURE 4. The relation between the number of glomeruli per kidney and the urea clearance test in chronic glomerulonephritis and arteriosclerotic Bright's disease

autopsy show a marked reduction, entirely comparable to that found in patients dying of chronic glomerulonephritis. There are normally about 1,250,000 glomeruli per kidney, and this must be reduced to below 500,000 and usually to below 300,000 before uremia develops (Fig. 4). These individuals are unable to excrete a urine above 1.010 or 1.012 specific gravity and have clearances of less than ten per cent of normal.

Phenolsulfonphthalein output is likewise markedly reduced, usually to less than five per cent in two hours. The urine volume is increased unless cardiac failure is present, and the urine may contain considerable numbers

of red cells. The hematuria differs from that of chronic glomerulonephritis, however, in this way. While in glomerulonephritis the hematuria is constant, day in and day out, in arteriolar nephrosclerosis it is usually intermittent, the patient showing a number of red cells for a day or so, and then voiding clear urine. This hematuria is much more frequently due to rupture of a small vessel in one of the papillae or in the lower urinary tract than to glomerular damage.

It should also be mentioned that uremia may at times be precipitated in patients with a fair amount of renal reserve by cardiac failure or an intercurrent febrile affection. Either of these may lead to an oliguria which, in the presence of moderate impairment of concentrating power, causes retention in the blood and the consequent train of uremic symptoms.

There is a second group of patients with hypertension who show marked renal impairment, usually at the time when they first come under observation. These are often spoken of as "malignant hypertension." They are usually young, at times in the teens, more often in the twenties or thirties. The blood pressure is apt to be very high, cardiac hypertrophy marked, hypertensive neuroretinopathy is present and the development of renal insufficiency rapid. At autopsy, in addition to arteriosclerotic changes, there is necrosis in the walls of the smaller arterioles of the kidney, and at times in other organs, and reactive changes in the glomeruli. The course is a rapidly progressive one, death in uremia usually taking place within a few months after the patient first comes under observation. Occasionally, patients with benign hypertension, and who have shown little or no decrease in kidney function over a period of years, undergo a sudden change for the worse, manifested by a sharp increase in the degree of hypertension and rapid diminution in kidney function. At postmortem examination, these patients also show the arteriolar necrosis characteristic of "malignant" sclerosis.

The cause of "malignant hypertension" is entirely unknown. Goldblatt has produced the clinical picture in dogs, as well as all the characteristic pathological findings, by severe constriction of the renal arteries It seems not unreasonable to assume that in humans the condition is likewise the result of profound sudden renal ischemia. But we are at present completely ignorant of the factors leading to such a rapidly developing renal ischemia.

Prognosis: The prognosis of essential hypertension, as far as the kidneys are concerned, depends upon the presence and degree of impairment of renal function. When a concentration test shows a maximum specific gravity below 1.015 or clearances below thirty-five per cent of normal in a young individual with hypertension the outlook is usually very poor. In such patients the renal impairment usually progresses rapidly to nitrogen retention and death in uremia within months or a year or two. In older individuals, past fifty, the tempo of the development of the renal lesion is usually much slower, so slow indeed that as has been emphasized above, these patients usually succumb from cardiac failure or cerebral accident before the renal lesion has progressed to the point of kidney insufficiency. An occasional patient develops significant nitrogen retention and tolerates

it remarkably well for relatively long periods, even a couple years. But once acute uremic symptoms have developed, particularly if there is accompanying heart failure, the end is not far off.

Treatment: Unfortunately, there is little that can be done for the renal lesion in essential hypertension. In the early stages, the present evidence indicates there is diminished renal blood flow, usually the result of arteriosclerotic narrowing of the smaller renal ateriolcs, while in the later stages there is a reduction in the number of nephrons. Neither of these are amenable to treatment at the present time. In the absence of nitrogen retention there is no evidence that restriction of meat or other protein in the diet, or of salt, has any effect either on the renal lesion or on the hypertension.

It must not be forgotten that essential hypertension is a chronic disease, and that prolonged protein restriction is apt to result in anemia, lowered plasma proteins, and other symptoms of malnutrition. Diuretics, aside from water, are usually ineffective. With loss of concentrating power, urine volume must be increased to prevent nitrogen accumulation in the blood, but as a rule little is to be gained by a fluid intake in excess of 3000 cc. daily. In cases with a tendency to cardiac edema and impaired concentrating power the dilemma is a real one, the renal condition calling for abundant fluid intake, the cardiac for its restriction. Under these circumstances an unsatisfactory middle ground is the usual compromise. Occasionally in such cases, one of the xanthine diuretics, theobromine sodium salicylate, theophylline, or aminophylline, are helpful. These must be given intermittently, for if administration is continued the diuretic action is lost. They are best prescribed in courses of two or three days with an equal time interval between. When there is any edema, or other evidence of cardiac failure, digitalis should be given in the usual manner. There is no basis for the fear that it will raise the blood pressure.

A considerable number of new drugs have been advocated in the treatment of hypertension.[43] These include preparations of rauwolfia serpentina and its alkaloids, various preparations of veratrum, and ganglionic blocking agents such as hydralazine and the methonium compounds. These are all potent drugs which will lower blood pressure if given in sufficient quantity. They are symptomatic remedies, and do not affect the underlying pathological process. Their use is discussed elsewhere in these volumes.

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ARTHUR C. DEGRAFF, M.D.
AND
A. M. OSHLAG, M.D.

29

Capillary Circulation

Introduction: The importance of the capillary circulation becomes apparent at once when one considers that the purpose of the circulation is to supply the cells of the body with the substances required for their metabolism and to remove the products of their activity, and that these interchanges occur only across the walls of the minute vessels. All vessels which permit this interchange may be classified as capillaries. However, in the strict anatomic concept, only the simple endothelial tubes can be so considered. Rather than confine the discussion to the true capillaries alone, the structure and function of the fundamental minute vascular pattern will be considered, since this represents the unit which carries out the ultimate purpose of the circulation, namely, the interchange of substances between blood and tissue cells.

Studies have shown that particular organs have their own modifications of the minute vessels. However, most of the capillary studies of the various organs have been made in animals, and it is primarily the skin capillaries that have been studied in man. Since analogous capillary circulations may be different in animals and man, and since changes in the skin capillaries may not be duplicated in other capillary beds of the body,[1] it is difficult to arrive at definitive conclusions. From the work which has been done, certain concepts seem apparent.

Capillary Patterns. *Nutritive Type:* Chambers and Zweifach[2,3,4,5] have recognized by the use of the micromanipulation technic that in addition to the specialized capillary beds of various organs, there is a basic nutritional pattern of blood vessels of the omentum, mesentery, skeletal muscle, intestinal serosa, and the subcutaneous tissue of the interdigital web of amphibia and mammals (Fig. 1). This structural capillary unit consists of a central channel which joins the terminal arteriole and the venule. The initial portion of this central channel is encircled with single discontinuous, typical muscle cells and is called the metarteriole. The remainder of the central channel is called the a-v thoroughfare channel. For a small distance along the proximal portion of the a-v channel there are discontinuous atypical muscle cells. The distal portion has no surrounding muscle cells. From the metarteriole and the proximal part of the a-v channel, branches come off abruptly. In the regions of the central channel

where muscle cells are present, these branches, at the junctional segment, also have muscle cells which are called the precapillary sphincters, and that portion of the vessel, the precapillaries. Where there are no muscle cells, as in the distal portion of the a-v channel, there are no precapillary segments, and the branches are true capillaries. The precapillaries quickly lose their muscle cells and become true capillaries, which may anastomose with each other and then rejoin the central channel in its distal portion. Each of these central channels with its side branches is considered a structural unit. However, capillaries of one unit may communicate with the capillaries of another. Occasionally, a capillary with a precapillary sphincter may originate directly from an arteriole. These offshoots branch

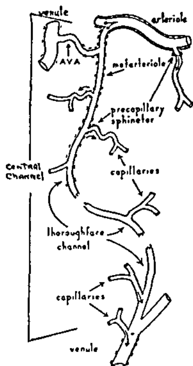


FIGURE 1 Diagram of a unit of the nutritional type of capillary bed, also showing a meta-arteriolar-venular anastomoses (A V.A.), and a precapillary branching directly from an arteriole (Modified from Chambers, R., and Zweifach, B W.: Am J Anat. 75:173 (Sept) 1944

into other capillaries and then reunite and re-enter *arteriovenous* capillaries. The ratio of the number of central channels to the number of capillary offshoots varies from tissue to tissue.

The central channels are not the same as the arteriovenous anastomoses, sometimes called Sucquet-Hoyer bridges.[2] The central channel is a relatively long vessel with capillary side-branches. The arteriovenous anastomoses are short muscular vessels which join the arterioles or metarterioles and veins (Fig. 1). They primarily act as shunts which may insure an adequate venous return, perhaps at the expense of the circulation in some of the capillaries in that region.

Chambers and Zweifach[2,3,4,5] also believe that the basic structural unit of the capillaries described above is also the functional unit of the nutritional type of capillary bed. In resting tissue blood flow through this capillary unit is intermittent. This is due to vasomotion, an alternate constriction and dilatation of the metarterioles and precapillary sphincters of the muscular portions of the capillary bed, which periodically varies the flow through the various components of the bed. If the constrictor phase of vasomotion, which may last from 10 to 120 seconds in duration, predominates, then the tissue is relatively ischemic. If the dilator phase predominates, more blood flows through the central channel, and since the precapillary sphincters are open, more of the capillaries have blood flowing through them, and the tissue becomes hyperemic. Vasomotion helps control the capillary circulation, and enables it to act independently of the rest of the circulation. There is no synchrony of vasomotion of neighboring metarterioles, or necessarily any between the parent metarteriole and the precapillaries. The vasomotion rhythm of a metarteriole is not constant and varies from time to time. An intact nerve supply is necessary for vasomotion,[2,3,6] cutting the vasomotor nerves or deep anesthesia will abolish it. The contractile portion of the capillary bed is also under hormonal or at least chemical control.[3] Epinephrine causes a marked constriction of the metarterioles and precapillary sphincters, although the latter are apparently more responsive. Histamine causes dilatation of approximately equal degree of both the metarterioles and precapillary sphincters.[7] Local trauma, variations in temperature, muscular exercise, and prolonged hypoxia tend to abolish vasomotion. Acute hemorrhage, sympathetic stimulation and intravenous epinephrine, or adrenal cortex extract increase vasomotion.[7]

Since the ratio of the number of central channels to the number of capillary offshoots varies from tissue to tissue, and since vasomotion can control the amount of blood flowing through the capillaries, those organs with a large percentage of capillary offshoots possess a tremendous potential of capillary circulation. This is especially true in muscle where the requirements of the circulation at rest and during exercise vary greatly.

In addition to the nutritive type of capillary bed described above, other patterns apparently related to *function* exist within particular organs.

Kidney: In the frog kidney, Richards and Schmidt[8] found that only a constantly changing fraction of the total number of glomeruli, or of the capillaries of a single glomerulus, possesses an active circulation. This fraction can be increased by vasodilators and decreased by vasoconstrictors.

Such an intermittency of glomerular circulation was not demonstrated in mammalian kidney (rabbit, dog) where all glomerular vessels were simultaneously active. Smith,[9] from his saturation studies of the kidney in man, demonstrated that the maximal glucose absorption and the maximal rate of tubular excretion of diodrast are not significantly altered by vasodilators and vasoconstrictors. He concluded that in man "an assumption of glomerular intermittency carried over from cold-blooded vertebrates is untenable." Truetta *et al.*[10] question this constant glomerular flow, and have described an alternate pathway for blood flow in

the kidney. This route is through the large juxtamedullary glomeruli which have large efferent vessels. These divide and become the vasa recta which, in turn, drain into the arcuate and interlobular veins. The vasa recta are of large caliber but structurally are similar to capillaries. This primarily medullary route in rabbits and rats may be used in varying degrees to short-circuit the cortical circulation and under certain conditions make glomerular circulation inconstant. These findings and their implications in certain disease states may be of great importance.

Lung: The superficial blood vessels on the surfaces of the air sacs of both the frog and the cat lung were studied with a transillumination technic without opening the pleura.[8] The number of capillaries through which the blood flows at a given time varies greatly and represents only a small fraction of the total number of the capillaries of the lung. The velocity of blood flow and the cell content of the blood vary even in capillaries arising from the same arteriole. Spontaneous reversal of the direction of circulation in the capillaries occurs and persists from seconds to minutes. In studies of CO uptake and elimination in man, Roughton[11] has estimated that the total volume of blood in the patent lung capillaries is about 60 cc. at rest and 95 cc. during hard work.

Skin: In the skin of man as well as of animals, an intermittent type of blood flow is demonstrated by direct observations over periods of time. Capillary counts in the skin of normal man, before and after intradermal histamine, reveal that only a fraction of the total number of capillaries is open at any one time. Lee and Holtze[12] report that the bulbar conjunctiva in man reveals a capillary bed not unlike that of the nutritive pattern described by Chambers and Zweifach. However, Grafflin and Corddry[13,14] were unable to confirm this typical pattern in the bulbar conjunctiva, although they found that intermittency of flow was present. In addition, they discovered arterio-arterial and veno-venous anastomoses along with a-v anastomoses. These same authors also failed to find a structural unit based upon a thoroughfare channel in the web and urinary bladder of the frog. Lutz *et al.*[15,16] did not find a central thoroughfare channel with their capillary branches in the cheek pouch of the hamster or in the retrolingual membrane of the frog, nor did Nicoll and Webb[17] find it in the subcutaneous tissue of the bat's wing. However, precapillary sphincters, vasomotion, and intermittency of flow are present in these capillary circulations.

Spleen: By a transillumination technic, a characteristic pattern of capillary circulation was found in the spleens of mice, rats, and cats[5] (Fig. 2). The central artery of the malpighian body divides into arterioles from which the capillaries arise. These capillaries are of two types; one continues directly to the collecting venule and the other becomes a sinusoid. Sphincters are present at both the afferent and efferent ends of these sinusoids, which, like the capillaries, are apparently endothelial tubes but larger and more irregular. Sinusoids may empty into the collecting venule directly or form a chain of sinusoids which then enter into the collecting veins. Capillaries which connect the secondary branches or penicilli of the central malpighian artery also anastomose with the long

straight capillaries which traverse the pulp and with the capillaries of the malpighian body itself. All of the capillaries as well as the sinusoids demonstrate an intermittency of flow. In the sinusoids this is controlled by the sphincters which may trap blood in a sinusoid and separate it from the rest of the circulation while plasma filters out, or the sphincters may allow the blood to flow freely through a sinusoid without hindrance.

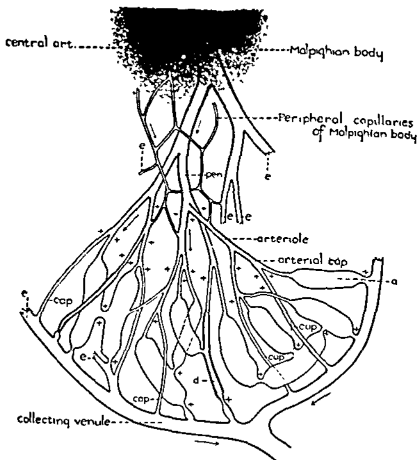


FIGURE 2. Diagram of the minute vessel pattern on the spleen The symbols indicate the following +'s, the positions of sphincters, arrows, the direction of blood flow; *a*, a dilated sinusoid; *d*, a sinusoid in a conducting phase; *cap*, capillaries, *pen*, a penicillus, and *e*, connections with other blood vessels not shown in the diagram (Modified from Knisely, M H Anat Rec 65·23 (April 25) 1936)

In the capillaries this intermittency is apparently controlled by the arterioles. Others have failed to observe the pattern of the minute vessels here described and believe that the capillaries open directly into the splenic pulp Such entry of red blood cells into the pulp may have been the result of trauma and the artificial circumstances (Fig. 2) of observation rather than a physiologic state Doggett[18] has confirmed the existence of a closed circulation in the dog spleen whereby the capillaries join the arterioles to the sinuses.

Liver: The livers in animals were studied with the transillumination technic of *Knisely.*[8] The terminal portions of both the hepatic artery and the *portal veins* may empty *independently into the sinusoid,* and an entire section of a liver lobule may be supplied by either purely arterial or purely portal blood. However, *in the main,* there is a mixture of portal and hepatic blood before it empties into the sinusoids. *Intermittency of flow* is also characteristic of this sinusoid *(capillary) circulation.* Not only does the number of active sinusoids vary *constantly* but *also the* type of flow in a particular sinusoid may change. About *seventy-five* per cent of the circulation is *inactive at one time.* The liver sinusoids in all parts of the lobules *actively* contract when epinephrine is applied locally or *via* the portal vein.[19]

Brain: The *surface capillaries* of the brain appear open at all times. Under *normal conditions,* the circulation in the brain is probably more *constant than* in other tissues because the activity of the brain is at a more constant level.

The conclusions from the data given above indicate that although the *capillary* circulations of the brain and possibly the kidney in certain *mammals* are constant, the capillary patterns of the skin, lung, liver, and *spleen* in the species studied have certain factors in common They are *characterized* by an intermittency of blood flow so that in the resting or *normal* state of the tissue a large percentage of the capillaries of the *particular* organ is inactive. This intermittency appears to be controlled by muscular elements which are either part of the capillary bed or part of the vessels leading into or out of the bed.

Intermittency of capillary blood flow appears to be an important physiological mechanism whereby blood flow to tissue is kept commensurate with *its* need, and whereby the blood volume fills a potentially large circulatory bed.

Capillary Anatomy: The true capillary is a simple endothelial tube surrounded by a perivascular supporting sheath of connective tissue in which are scattered the noncontractile Rouget or extraendothelial cells. It has a noncellular lining possibly derived from the blood proteins. The endothelial cells which have all the fundamental attributes of living cells are bound together at their edges by the intercellular cement. Chambers and Zweifach[7] concluded that the intercellular cement is produced by the endothelial cells and is a calcium salt, possibly a calcium proteinate. Some investigators have postulated that the intracellular cement is an important part of the capillary membrane across which *materials are* exchanged.[20] Variations in the porosity of the intercellular *cement* would therefore help govern the passage of material.

Although individual endothelial cells may contract under manipulation, *the consensus is that* the capillary is noncontractile.[2,3,6,22] India ink injected[21] *under increasing* pressure into a capillary closed at both ends *escapes through localized* areas of the endothelium although no tears of the wall are seen, indicating that the capillary wall is "not a uniformly resistant membrane." This is also demonstrated by the appearance of red

blood cells in the lymph during exercise and by the escape of leukocytes and erythrocytes from capillaries in the inflamed areas.

Passive changes in the capillaries may have been misinterpreted as active contractions. Since the living endothelium has an inherent elasticity, an increased blood flow may distend the capillary which resumes its original size as blood flow decreases.[2,6] If an inactive capillary is between two vessels with an active circulation, a suction or aspiration

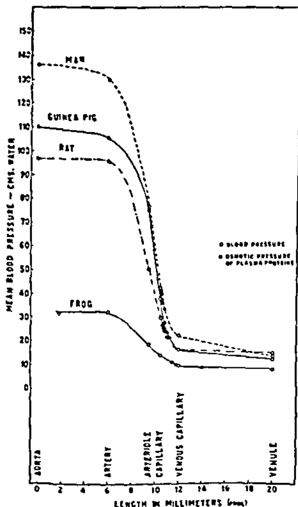


FIGURE 3. Chart showing relation between capillary blood pressure and the osmotic pressure of the plasma proteins in four species (Landis, E. M.: Physiol. Rev. 14:404 (July) 1934.)

effect may decrease its diameter.[4,5,6] Alteration of capillary size may occur by growth of the vessel itself. This change occurs slowly and is apparently related to the blood "load" that the capillary carries over long periods of time. Clark and Clark[6] believe that not only can the number of cells change, but the tonicity of endothelial cells may increase with a resultant narrowing of the endothelial lumen.

Physiology. ***Capillary Pressure:*** The blood within the capillary exerts a hydrostatic pressure which has been measured by direct and indirect methods. The direct method which is the more accurate and considerably more difficult, although not free from criticisms, depends on the introduction of a micropipette into the capillary. In the many indirect methods which are essentially similar, graded pressure is applied to the tissue until blanching is produced, or some phase of cessation of capillary flow is noted microscopically. The indirect methods are considered to be unreliable; readings do not compare satisfactorily with those obtained by microcannulation.

Landis[23] showed that there is a pressure gradient in the capillary which varies with the species. This gradient is part of the general decrease in blood pressure which occurs from the aorta to the large veins (Fig. 3). The capillary pressures of the species studied were all within the range of their particular colloid osmotic pressure.[21,24] The pressure of the capillaries is extremely variable. It may vary from moment to moment in the same capillary and differ in the various capillaries of the same network at the same time. These variations may cause the capillary pressure to be above the colloid osmotic pressure at one moment and below it at another. In the skin of man this gradient varies from approximately 33 mm. Hg at the arteriolar end of the capillaries to 12 mm. Hg at the venous end.

Several factors have been shown to affect capillary pressure. Hyperemia, as from local heat, causes an increased blood flow to a part, an increase in capillary pressure, and an increase in the pressure gradient. A decreased flow to a part, as from arteriolar constriction due to cold, results in a fall in capillary pressure and a decrease of the pressure gradient. An elevation of venous pressure produces a rise in capillary pressure until it just exceeds the venous pressure. In order to obviate hydrostatic effects in its measurement, capillary pressure, like venous pressure, must be measured at the level of the right auricle.

Poiseuille's law can only approximate the pressure fall in capillaries. The continually varying diameter of the capillaries as a result of vasomotion and changing tissue pressure,[25] the anomalous viscous properties of plasma at low rates of flow in small capillary tubes,[26] and the presence of cells in the blood are all factors which make the law difficult to apply.

Forces Effecting Capillary Filtration: Materials are exchanged between the circulating blood and the extracellular fluid primarily over the capillary membrane. This interchange[21,27] depends on the resultant of the forces favoring and those opposing filtration, the area over which filtration takes place, and the capillary permeability. The latter may be defined as the ease or ability with which a substance passes through the capillary wall under standard conditions. Permeability, therefore, is but one factor in filtration. Although most substances pass through the capillary wall, it is relatively impermeable to large molecules like the plasma proteins. As a consequence of being retained by the capillary wall, the proteins exert a pressure called the colloid osmotic pressure.

The resultant of the forces affecting fluid movement depends on four

factors[21,27] (Starling's hypothesis): (1) The colloid osmotic pressure of the blood; (2) the capillary hydrostatic pressure; (3) tissue pressure; and (4) the osmotic pressure of the small amount of protein in the extracellular fluid. The hydrostatic pressure and the extracellular fluid osmotic pressure favor outward filtration of fluid. The colloid osmotic pressure of the blood (oncotic) and the tissue pressure favor absorption.

Along an individual capillary with its gradient of hydrostatic pressure, the filtering forces are usually directed outward at the arteriolar end of the capillary and inward at the venous end. Vasomotion may modify fluid exchange since it can regulate the hydrodynamic pressure in the capillaries.

Permeability of Capillaries: The exchange of materials through the walls of the capillary is considered to take place by physical processes which involve no expenditure of energy on the part of the capillary wall itself. Although the mechanisms by which this exchange occurs are still under investigation, the forces involved in the exchange of water appear largely related to filtration and diffusion.[20,28] Filtration is the passage through a semipermeable membrane of an ultrafiltrate without separation of the constituents of the fluid, except in so far as large molecules like proteins are held back by the sieve-like structure. According to one investigator, Poiseuille's equation is assumed to apply to flow through these pores and filtration occurs because of the gradient of hydraulic pressure.[20] Diffusion is the passage of a given substance, a molecule or a particle, at a given time in the direction of the gradient of its chemical or electrochemical potential. The rate of net passage of a solute through a membrane would be proportional to its diffusion coefficient in the membrane. Filtration and diffusion are therefore different phenomena.

Diffusion does play an important role in the transcapillary exchange of materials. Hyman *et al.*[29] found that clearance rates of Na^{24} and I^{131} when injected subcutaneously in man are not appreciably affected by concurrent edema formation. Chinard *et al.*[28,30] injected solutions of substances of different molecular weights into an artery of a region and then collected samples from the vein of that region They found that the materials of higher molecular weights were concentrated in the venous samples. As diffusion rates are proportional to molecular weight, these results indicate that diffusion was occurring Radioactive substances were used in similar type experiments with comparable results

Keys[21] determined that certain crystalloids did not pass through the capillary membrane as rapidly as water, but that their rate of passage was inversely proportional to molecular size During exercise, the osmotic force developed in muscle increases markedly. The slight delay in the passage of these crystalloids through the capillary wall would, however, provide a potent mechanism of "osmotic buffering" This would prevent a tremendous loss in water from the blood stream in exercise or in any other condition associated with shifts of osmotic pressure on either side of the capillary wall However, several studies showed[20] that different radioactive substances of different molecular diffusion coefficients and charge disappeared from the arterial plasma at about the same rate Blood flow as well as capillary permeability may, of course, be a limiting

factor where diffusion is rapid. Chinard[30] developed a diffusion hypothesis for the passage of material through the glomerular capillary wall, and concluded that the passage of water involves most of the capillary surface.

Pappenheimer *et al.*[20,24,31,32,112,113,114] studied hind limbs of cats perfused with cat-blood to which test substances were added. Their extensive data permitted computation of the capillary wall area per unit length of capillary vessel available for the diffusion of the test substances; that area is constant for diffusing a given substance and is independent of blood flow but decreases with increasing molecular size. About 0.2 per cent of the capillary wall surface area participates in the exchange of water and lipid-insoluble molecules. The porosity of the capillary wall is considered to be uniform and the pore population is estimated at 1-2 billion/cm.

Filtration and diffusion determine transcapillary movement of all substances. Diffusion, although overwhelmingly faster, is "*restricted*" however, by the relationship between the assumed constant pore size and the size of the diffusing molecule so that specific molecular "sieving" is observed for a given substance. As the size of the molecule increases, diffusion of the substance becomes more restricted and filtration assumes a more prominent role in the translocation of the substance across the capillary wall. How much a substance will be "*sieved*" is determined by the ratio between the restricted diffusion coefficient and the rate of filtration of the substance in question. Obviously, the smaller the molecule the lesser the restriction to diffusion, the lesser the concentration gradient between blood and tissue fluid, and the lesser the "sieving." This is true for NaCl as an example; conversely, plasma protein molecules are "sieved" to a much greater extent resulting in marked intravascular conservation of protein. If the rate of filtration is abnormally low, then diffusion equilibrium with extracellular fluid may be expected even for large molecules like proteins.

Their data also suggested that gases and lipid-soluble molecules traverse the endothelial cell and are not restricted for their passage to the intercellular spaces of endothelium.

Several workers have demonstrated that electrical charge may be related to permeability. Friedemann[33,34] found that substances to which the capillaries of the brains of certain animals were impermeable, were negatively charged (acid), while positively charged (basic) materials passed through the brain capillaries readily. This may be one reason why tetanus, botulinus, staphylococcus and diphtheria toxins do not penetrate the brain capillaries. The reverse is true for the choroid plexus, ciliary plexus and capillaries of the peritoneum. Most other capillaries are permeable to both electropositive and electronegative substances, although more permeable to the former. No conclusions can be reached at present, but other factors as electro-osmosis, etc., may certainly play a role in permeability.

Permeability of the capillaries as noted above, varies in different tissues,[35] and apparently by various mechanisms. The capillaries of the extremities are estimated to be ninety to ninety-five per cent efficient in

retaining protein. In the liver and intestines the capillaries[21] are much more permeable to protein and osmotic pressure probably plays little part in fluid movement. Newly growing capillaries are more permeable to protein and dyes, than older ones.[30] Hechter,[1] in studying capillary permeability, found that histamine applied through a stab wound in the skin of rats allowed trypan blue to accumulate at the area. However, no fixation occurred in the gastrocnemius muscle after histamine injection or after the local application of xylol. Trauma did cause the dye to be fixed in the muscle.

Local injury apparently from any source results in an immediate increase in "permeability" of the capillaries.[21] Heat and cold, if sufficiently severe, lead to the formation of blisters and apparently an increase in capillary "permeability" as the fluid of the blister contains an increased amount of protein.[21] In the perfused hind limb preparation of cats[20] temperature changes from 8° to 44° C. (46.4° to 111.2° F.) apparently have no effect on capillary "permeability." Studies on the effect of temperature on fluid-exchange in the human forearm indicate that filtration is altered with changes in temperature. However, viscosity changes with temperature, a change in the available area of the capillaries for filtration, and changes in the ratio of arteriolar to venular tone with its effect on mean capillary pressure, may be factors which may have altered filtration without necessarily altering capillary permeability.[20] Hyaluronidase[7] apparently does not affect capillary permeability, but does cause an increased capillary fragility Oxygen-lack of moderate degree has little effect on the capillaries in animals.[21,37] Clinically, patients with marked cyanosis do not manifest any evidence of increased capillary "permeability" as indicated by the absence of edema. Furthermore, the low protein content of the edema of edematous patients with arterial oxygen saturations of fifty to sixty per cent of normal indicates that capillary "permeability" has not increased. Severe anoxia, however, such as may be seen clinically in an acute total arterial obstruction, causes an increase in capillary "permeability."[38]

Many[7] attempts have been made to measure the effect of various agents on capillary "permeability." A common method of study is to observe the loss of dye from the blood into the skin during a locally produced inflammatory reaction, and then to note the effects of various locally introduced agents in altering the escape of dye. It is difficult to evaluate whether these agents affect capillary true permeability or some other function associated with the local inflammation or with the stainability of the tissue, etc.

According to Chambers and Zweifach,[7] histamine given locally or intravenously in sufficient concentrations produces arterial dilatation and damage to the capillary endothelium Changes in capillary "permeability" were noted only with concentrations high enough to produce actual endothelial damage. However, the last phase of the well known triple response is the wheal, which results from an increase in capillary "permeability," as indicated by the high protein content of the edema fluid. According to Lewis, this is due to the liberation of a material called H substance

which is similar to, or identical with, histamine. These not been reconciled. It is not known to what extent normal permeability. Most indirect studies indicate that increased capillary permeability. An additional effect c noted when it is painted on the skin of mice. The capi. cells become phagocytic for carbon particles when India intravenously. Injury to the skin produces the same phei endothelial cells. This effect is inhibited by an antihistami

The products of inflammation, leukotoxin[40,41,42] and e exotoxin of clostridium oedematiens,[21,117] also increase cap bility. After injection or direct application, there is a de. hours before the effects of the exotoxin are noted in th "foreign"[43] plasma also contains a material that increa permeability.

Studies indicate that adrenal cortex preparations, ACTH ai decrease capillary permeability.[40,41,42,44,45,46,47]

Reactive hyperemia is the dilatation of blood vessels and th blood flow which follows the release of an occluded peripheral a flushing that is associated with this phenomenon is due to tl of normally non-functioning capillaries that are full of blood. In the capillaries of the nailfold in man, Eichna *et al.*[48,49,50] found t lary pressure following reactive hyperemia remained remarkably and that the markedly increased blood flow did not alter capillary as might be expected. This may be because of the presence of a- as well as because of the increase in the number of open capillari

Reactive hyperemia[26] has been attributed to the accumulatic the temporary ischemia of local vasodilator metabolites as histam substances. However, antihistamines did not inhibit reactive hyp Decreasing blood flow by raising venous pressure did not produce re hyperemia, nor did the use of inhalation mixtures with low oxyge. high carbon dioxide tensions increase blood flow. Blood vessels whic repeatedly occluded lose their ability for reactive hyperemia, but the still responsive to histamine and other vasodilators, and oxygen consu tion remains unchanged. These studies[26] have suggested that the arteri dilatation that occurs in reactive hyperemia is secondary to decreas the arterial intravascular tension and elimination of the normal mus stretch stimulus of the blood pressure in maintaining the arteriolar to. Other studies have related the phenomenon to acetylcholine. Iodoaceta which inhibits reactive hyperemia in muscles and fluoroacetate whic increases reactive hyperemia have similar actions on the vasodilatin property of acetylcholine.

In frogs[7] the addition of particulate material to the perfusing fluid leads to a more normal type of capillary circulation, and prevents edema for longer periods of time than perfusion fluid without the added materials. This result is thought to be due in part at least to a mechanical plugging of the pores. The plasma proteins may reduce the filtration of fluid by coating the capillary endothelium.[27] A normal concentration and type of plasma proteins may be necessary for normal capillary permeability.

In rabbit muscle, acid vital dyes, particularly poorly diffusible dyes, pass out of the capillaries most readily in the region where they unite with the venule.[21] This gradient of permeability extending along the capillary does not increase enough to allow protein molecules to pass. It is not affected by plethora, exercise, shock, injections of epinephrine, or pituitrin. Rous, Gilding, and Smith believed that by this mechanism "food stuffs" can be supplied equally well to all parts of the tissue, since no gradient of permeability was found where the anatomic arrangement of the capillaries was such that it insured a uniform supply of the diffusible constituents. Since the direction of this gradient in permeability can be reversed if the blood is rerouted so that it goes from the venous to the arteriolar end of the capillary,[4] and since the permeability gradient is obliterated in urethanized frogs by sympathectomy, it would appear that the gradient is not a function of the anatomy of the vessel. Heimbecker *et al.*[51] found that reversing the blood flow in the mesenteric capillaries of cats did not alter oxygen uptake.

The importance of tissue pressure should not be underestimated. On standing, the capillary pressure is increased by a hydrostatic pressure equal to the distance from the right auricle to the capillaries concerned. This increase in hydrostatic pressure is considerable and would greatly increase fluid filtration from the blood. However, the tissue pressure which is also increased on standing, imposes a counterforce which prevents rapid filtration and edema formation.[52] Landis and Gibson[21] demonstrated that tissue pressure reduces filtration due to an increased venous pressure, and that an increased tissue pressure increases the rate at which extravascular fluid is removed from tissue spaces. Burch[53] found that the tissues around the eyes which become edematous early in disease have a low tissue pressure. Accumulation of tissue fluid and elasticity of tissue play influencing roles in the development of tissue pressure.

The passage of fluid into or out of normal tissue[52] occurs in an intermittent manner and is apparently related to the changes of flow and pressure which are part of the capillary circulation. When McMaster[52] introduced fluid into the tissue spaces at atmospheric pressure, he found that the fluid was taken up more rapidly during hyperemia than in normal tissue but still in an intermittent manner. When the venous pressure in a tissue is increased, there is a reversal of the flow of fluid out of the tissue and into the testing apparatus, but the fluid movement is still intermittent. In contrast to this, when fluid is introduced into tissues without circulation, the fluid flows in continuously.

Sludge: Knisely and his coworkers[54,55,56,117] have studied the flow of blood in the small vessels of the organs of animals and of the bulbar conjunctiva of man by means of the fused quartz-rod technic and by the dissecting microscope. In the blood vessels of normal tissue, they noted that the erythrocytes tended to repel each other, that blood flow was laminar, and that the inner surfaces of the vessels were smooth and clear. The vessels were not observed to leak any appreciable amount of fluid. In the vessels of 60 to 120 microns in diameter, blood flow was so rapid that individual red blood cells could not be seen. The diameters of the

which is similar to, or identical with, histamine. These observations have not been reconciled. It is not known to what extent histamine alters normal permeability. Most indirect studies indicate that histamine causes increased capillary permeability. An additional effect of histamine[39] is noted when it is painted on the skin of mice. The capillary endothelial cells become phagocytic for carbon particles when India ink is injected intravenously. Injury to the skin produces the same phenomenon in the endothelial cells. This effect is inhibited by an antihistamine drug.

The products of inflammation, leukotoxin[40,41,42] and exudin and the exotoxin of clostridium oedematiens,[21,117] also increase capillary permeability. After injection or direct application, there is a delay of several hours before the effects of the exotoxin are noted in the frog. Fresh "foreign"[43] plasma also contains a material that increases capillary permeability.

Studies indicate that adrenal cortex preparations, ACTH and cortisone, decrease capillary permeability.[40,41,42,44,45,46,47]

Reactive hyperemia is the dilatation of blood vessels and the increased blood flow which follows the release of an occluded peripheral artery. The flushing that is associated with this phenomenon is due to the opening of normally non-functioning capillaries that are full of blood. In studying the capillaries of the nailfold in man, Eichna *et al.*[48,49,50] found that capillary pressure following reactive hyperemia remained remarkably constant and that the markedly increased blood flow did not alter capillary pressure as might be expected. This may be because of the presence of a-v shunts as well as because of the increase in the number of open capillaries.

Reactive hyperemia[26] has been attributed to the accumulation from the temporary ischemia of local vasodilator metabolites as histamine-like substances. However, antihistamines did not inhibit reactive hyperemia. Decreasing blood flow by raising venous pressure did not produce reactive hyperemia, nor did the use of inhalation mixtures with low oxygen and high carbon dioxide tensions increase blood flow. Blood vessels which are repeatedly occluded lose their ability for reactive hyperemia, but they are still responsive to histamine and other vasodilators, and oxygen consumption remains unchanged. These studies[26] have suggested that the arteriolar dilatation that occurs in reactive hyperemia is secondary to decrease of the arterial intravascular tension and elimination of the normal muscle stretch stimulus of the blood pressure in maintaining the arteriolar tone. Other studies have related the phenomenon to acetylcholine. Iodoacetate which inhibits reactive hyperemia in muscles and fluoroacetate which increases reactive hyperemia have similar actions on the vasodilating property of acetylcholine.

In frogs[7] the addition of particulate material to the perfusing fluid leads to a more normal type of capillary circulation, and prevents edema for longer periods of time than perfusion fluid without the added materials. This result is thought to be due in part at least to a mechanical plugging of the pores. The plasma proteins may reduce the filtration of fluid by coating the capillary endothelium.[27] A normal concentration and type of plasma proteins may be necessary for normal capillary permeability.

years of age.[60,61] Birth weight is positively correlated with resistance which is quite low in premature infants. In the r maturity of the capillary bed and apparently of the surrounding tissue seems to be of importance in determining capillary re Jaundice, sex, and the antenatal administration of vitamin K a not apparently affect capillary fragility. In the newborn, no variation is noted in contradistinction to observations in child adults where capillary resistance is lowest in spring and highest i

In pregnant women, a decrease in capillary resistance occurs term followed by a rise during labor and the puerperium to a leve than in normal controls. There is no correlation between capillar ance of mother and child.[61]

Capillary resistance varies in different parts of the body, but is higher in the lower portions than in the upper.[62,118] A decrease i lary resistance has been noted in some women just before the fi of menstruation.[62,63]

Histamine given subcutaneously or intravenously in flushing causes an almost immediate decrease in capillary resistance with a to normal in a short time followed by higher than normal levels.[6] action of histamine may be inhibited by an antihistamine drug a adrenalin, the latter being the more effective. Hyaluronidase also an increase in capillary fragility.[7] Calcium salts intravenously, adr and insulin cause a marked transient increase in capillary resistanc ACTH and cortisone also cause an increase in capillary resistanc will prevent the increase in capillary fragility noted in the Schwar phenomenon both at the local site and generally if given two hours l the intravenous provocative dose. The effect of many drugs or proce causing an increase in capillary resistance may be due to the relea endogenous ACTH.[66] Radiation has been reported as causing increased and decreased capillary fragility.[65] Dosage may be the dec factor.

In a study of forty-eight patients with various allergies, no abnorm was found in capillary resistance,[67] but in an area of urticaria the capi resistance has been found lowered.[62]

In purpura[68,69] of any etiology and regardless of the presence or abs of thrombocytopenia, there is increased capillary fragility. In ce purpuras, studies have suggested that the capillary endothelium platelets are antigenically related. ACTH and cortisone decrease capil fragility apparently in all types of purpura, but only irregularly incr the number of platelets.

In patients with scurvy, capillary hemorrhage occurs without any visi anatomic basis. Alterations in the intercellular cement and in the pe capillary sheath have been suggested as the basis for the hemorrha In[70] experimental human scurvy, direct microscopic examination of h follicles of the leg revealed the appearance of new capillaries looped ab ... These capillaries then become dilated and eryth

Humble,

scurvy, used the tourniquet test and noted that hemorrhage occurred at the arteriolar segment of the capillary loop where pressure is highest. Lee[73] noted that petechiae in scorbutic guinea pigs that resulted from trauma occurred primarily in the venules rather than the capillaries From his additional observations of the blood vessels of the bulbar conjunctiva in man and of the petechiae produced in the cheek pouch of the hamster, he concluded that petechiae primarily occurred in the venules. The difference in observations of the location of petechiae has not been resolved.

Other diseases as scarlet fever, hypertension, and diabetes also show an increase in capillary fragility. In diabetes,[74] antihyaluronidase, given subcutaneously, decreased this fragility. In the retinopathies, hemorrhages are noted frequently. In diabetic retinopathy, capillary aneurysms



FIGURE 4 Photograph of capillaries of nail bed (Strax, P., and DeGraff, A C.: Am Heart J 6 807 (Aug) 1931)

are present in the deeper plexi of vessels.[75,76,77] These as such are not found elsewhere in the body. However, the lesions in the kidney in intercapillary glomerulosclerosis have been suggested as being related to a similar pathological process.

Flavinoids, as rutin, quercetin, hesperedin, esculin, and catechin, have a vitamin P activity which is reported as having some effect in decreasing capillary fragility and permeability.[78] The flavinoids are reported as capable of potentiating ascorbic acid activity, inhibiting the action of hyaluronidase, inhibiting the oxidation of epinephrine, and reducing the toxicity of histamine, possibly by inhibiting the action of histidine decarboxylase. These reactions are suggested as mechanisms by which the flavinoids might decrease capillary fragility and permeability in conditions. However, clinical reports of the success of these are not conclusive, although recommended in many diseases with decreased capillary resistance. Some investigators attribute the of rutin to its vasoconstrictor effects,[26] rather than to changes in fragility.

Orbison[79] in studying two patients with thrombotic thrombo purpura found vascular degeneration and aneurysm formation

arteriolar-capillary junction in the same general area where Humble noted hemorrhage.

Toluidine blue and protamine sulfate have been employed with some success in controlling petechial hemorrhages in certain patients with thrombocytopenia, leukemia, certain cases of menorrhagia in some patients and dogs exposed to lethal dosages of ionizing radiation, and in anaphylactic shock. It has been suggested that the effect is due to the ability of toluidine blue and protamine in counteracting the action of heparin or heparin-like substances. They apparently have no effect on the capillary itself.[80]

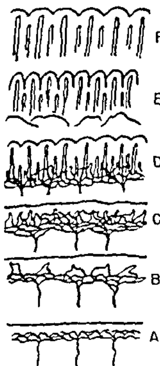


FIGURE 5 Diagram of development of skin capillaries *A*, primitive network with flat corium (at birth), *B*, *C*, beginning of loops (at five to six weeks), *D*, *E*, formation of hairpin loops, scalloping of corium, loss of subpapillary plexus, and *F*, mature form (Modified from Leader, S D , Am. J. Dis Child 44 403 (Aug) 1932)

The capillaries in diseased states in man have been studied almost exclusively in the skin, chiefly in the nail bed capillaries (Fig. 4). [illegible]

and gradually become [illegible] not appear in large numbers until the fifth month, and the adult pattern is complete at about one year. The horizontal capillary network, from which these capillary loops are derived, decreases in size and complexity

and the corium becomes scalloped. The capillary morphology then remains constant, although the loops may lengthen and become tortuous with advancing age.

Children with arrested mental development tend to show a retarded development of the skin capillaries, with abnormal infantile forms. This correlation is less striking when the physical development is normal.

Endocrine factors may play a role in capillary development since children with hypopituitarism or Froehlich's syndrome, or mxyedema, also show arrested skin capillary patterns, often with bizarre forms. In myxedema, the administration of thyroid causes a return of the capillary picture toward normal. In adults with myxedema, the nail bed capillaries can only be distinguished with difficulty as fineline structures, but with thyroid therapy the appearance approaches normal. An increased capillary "permeability," disappearing following proper treatment, has been reported in myxedema.[82]

The Capillaries in Diseased States: In patients with hyperthyroidism the skin capillary counts increased on an average only sixteen per cent per unit area after histamine injections, as compared with the average 120 per cent per unit area in that of the controls. This indicates that in hyperthyroidism, almost all the skin capillaries are open. There is no correlation between the percentage of open capillaries and the basal metabolic rate.

A large percentage of patients with idiopathic epilepsy, migraine, and schizophrenia reveal an immature arrested formation of the skin capillaries.[83,84] In contrast, many patients with manic depressive psychoses have skin capillaries with a twisted appearance not unlike those frequently seen in neurotic individuals.[83,85]

In multiple sclerosis, the nail fold capillaries, although not diagnostic, are frequently noted to be abnormal. The capillary loops are thin and small with "button-like" nodules at the summit or with a widened intermediate section of the loop. Blood flow is slow and irregular.[86]

Studies in patients with migraine while[87] having a headache revealed *an impaired visibility of the lip and nail fold capillaries. This blurring* was relieved by the intravenous administration of ergotamine tartrate. Migraine which was precipitated in twenty-one of twenty-nine patients after water ingestion diuresis had stopped, revealed this same blurring in about half of the patients. These changes have not been correlated with present theories of migraine.

In polycythemia vera the number of open capillaries per square millimeter of skin is fifty per cent greater than in normal subjects, and the area occupied by the blood in the capillaries per square millimeter is twice that of normal. This increase in capillary area is due in part to an increase in the number of patent capillaries and in part to dilatation of the capillaries primarily at their venous end. The skin capillaries seem to assume a storage function by dilating and increasing the number which are patent.

In Raynaud's disease,[88] the capillaries of the nail bed are usually abnormally large loops. In these capillaries, *the gradient of pressure* is

less than 3 mm. Hg instead of the usual 20 mm. Hg. Sympathectomy increases the pressure in the arterial limb only slightly and the gradient remains about 6 to 7 mm. Hg. During the vasospastic circulatory arrest, many of the nail fold capillaries become more widely dilated, lose their smooth outlines and demonstrate irregular indented contours. The blood in these capillaries becomes stagnant and more viscid, apparently by the loss of fluid, and capillary pressure falls to about 10 mg. Hg. When vasospasm is released, blood flow starts again and capillary pressure returns to values of 24 to 40 mm. Hg. In some of the capillaries, as blood flow is resumed, stationary erythrocytes appear beyond the summit of the capillary.[88] They are intracapillary and apparently adherent to the wall which becomes sticky during the vasoconstriction. The vasospasm in Raynaud's disease is considered to be precapillary in origin because during circulatory arrest, fluid injected into the capillaries easily drains out of the venous limb, and the pressure in the capillary still changes in response to alterations in venous pressure.

In acrocyanosis, the capillaries are large and dilated and flow is sluggish.

In certain skin diseases, the relation of the capillaries to the skin structures is quite typical.[89]

In psoriasis, the crests of the capillary loops are coiled into rather uniform ball-like structures which are spaced quite regularly. At the edge of the lesion the capillaries are dilated but normal in shape.

In lichen planus,[89] there is a central plaque of varying shape, surrounded by a border of hairpin shaped, slightly elongated and dilated, regularly arranged capillary loops which slant inward toward the central plaque. In the center of some large plaques where a brownish mass may be present, a thick horizontal S shaped loop or a few large diffuse capillaries are seen.

In discoid lupus erythematosus,[89] there are "thick clumsy loops" of capillaries running horizontally and obliquely about the keratotic plugs.

In scleroderma[50] secondary [illegible]
and behave as do the capillari[illegible]
In primary scleroderma involving the hands (acrosclerosis), the capillaries of the nail bed are huge loops, especially dilated on the venous side, and decreased in number up to about one-third that of normal. The reduction of the number of loops seems to be directly proportional to the degree of trophic disturbance. The outlines of these huge capillaries appear frayed, but no stasis is present and the blood flow is apparently relatively normal.[89] In the skin lesions there is pigmentation about the papillae of the skin and a normal capillary tip is seen in the center of the papilla.

In erythromelalgia, Wright and Duryee state that "capillary loops may be gigantic, grotesque, and irregular in form." The blood flow is exceedingly sluggish and stagnant pools of blood may form at the ends of the capillaries, helping to produce the changes in the color of the skin seen in this condition

The low protein content of the edema fluid[21,52] and the normal diffusion of fluoroscein dye[53] in patients with congestive heart failure indicate that

there is no increase in capillary "permeability." An elevated capillary pressure was found in the nail fold capillaries in the patients with heart failure.[90] What part this plays in the total edema formation remains to be determined.

Capillary counts in heart muscle[91] indicated that in cardiac hypertrophy the muscle fibers enlarge but the capillaries do not increase in number; there is actually a decrease in the ratio of capillary count to total muscle mass. In atrophied hearts the reverse is true; the muscle mass is decreased, and the capillary counts remain unaltered.

In acute diffuse glomerulonephritis,[53] the protein content of the edema fluid is low indicating that there is no increase in the peripheral capillary "permeability." The edema is believed by some to be due to water and sodium retention by the kidney. In the nephrotic syndrome, the peripheral capillary "permeability" is considered to be normal.[92] However, the glomerular capillary permeability is thought to be increased.[93]

It has been long thought that the causative agents of shock caused the capillaries to dilate and became hyperpermeable. Blood then sequesters in the capillaries and plasma leaks into tissue space, causing a continued reduction in the effective blood volume and, therefore, in the oxygen carrying capacity, until the compensatory mechanisms are no longer effective. Actually, there is little evidence of capillary stagnation early in shock.

Shorr *et al.*[94,95] found that the shock syndrome produced in anesthetized animals by hemorrhage or trauma could be divided into two stages. The first, or vasoexcitor stage, is characterized by increased vasomotion of both the metarterioles and the precapillary sphincters and by their increased sensitivity to epinephrine. This restricts capillary circulation to the central channels and helps maintain an adequate venous return. As the shock is prolonged, the initial response is superceded by the second stage in which the metarterioles and precapillary sphincters lose their vasomotion. Blood flow is now no longer confined to the central channel but spreads out into all the capillaries. This in turn leads to a sluggish capillary circulation and eventual failure of venous return. Once this condition is reached the shock is irreversible and the animal cannot be saved. The first, or compensatory phase, is associated with an hormonal factor called the vasoexcitor material (VEM) and the second, or decompensatory phase, is associated with an hormonal factor called a vasodepressor material, or VDM, which has been identified as ferritin. VEM is formed in the kidney under anaerobic conditions and inactivated in the kidney under aerobic conditions. VDM is formed in skeletal muscle and liver under anaerobic conditions and is inactivated by the liver under aerobic conditions or is excreted by the normal kidney. This concept stresses the importance of the capillary bed. However, other factors have also been associated with irreversibility.[95]

Although with the indirect technic both normal and high capillary pressures have been obtained in patients with hypertension, the directly determined digital capillary pressures in patients with essential hyper-

tension and in normal individuals rendered hypertensive by paredrinol sulfate were within normal values.[48,49]

Eichna and his associates, impressed with the constancy of capillary pressures regardless of the alterations in arterial and arteriolar flow, thought that a buffering mechanism must be present. This, they considered, might be the a-v shunts. Local injection of histamine in contrast to reflex vasodilatation and reflex hyperemia was able to raise the digital capillary pressure above that of normal patients, apparently by decreasing the precapillary vascular resistance. Observations of the bulbar conjunctiva in hypertensive individuals have revealed increased spontaneous vasomotion, metarteriolar narrowing, a decreased velocity of the peripheral blood flow, an increased tortuosity of many of the blood vessels, and an increased sensitivity of the metarterioles and precapillary sphincters to topically applied epinephrine.[96] Nail bed capillaries in hypertensives also revealed an increased sensitivity to intravenous epinephrine and especially intravenous nor epinephrine.[97] However, normotensives with hyperglobulinemia from multiple myeloma and some patients with Laennec's cirrhosis also showed an increased sensitivity of the metarterioles and precapillary sphincters to topically applied epinephrine in the conjunctiva.[98] Animals made hypertensive by the Goldblatt technic revealed changes in the mesenteric capillaries similar in nature to changes of the bulbar conjunctiva of hypertensive individuals

VEM and VDM which act on the metarterioles and precapillary sphincters in an opposing manner were found to be present in experimental hypertension [98] Following the application of the Goldblatt clamp, VEM was found in the renal vein and then in the systemic circulation. While the blood pressure continued to rise, VEM continued to be detectable. In the chronic phase of the hypertension, the blood, although apparently neutral in action, was so because the high titer of VEM was opposed by an equally high titer of VDM The significance of these changes is as yet unknown.[99] In ninety patients suffering from a variety of diseases, VEM and VDM were also found in the blood No causal relationship of these substances to high blood pressure is apparently present. Byrom[100] studied hypertensive encephalopathy in rats He concluded that severe focal arterial spasm occurred as a result of the hypertension. This severe arterial spasm depending on its duration, intensity, and extent could cause an increased capillary permeability with its associated focal edema or it could result in necrosis of the arterial wall or of the tissue supplied by the artery No explanation of the generalized edema of the brain that occurs late in these animals is known

Scheinker[102] in a pathologic study of malignant hypertension showed that at least in some of the cases capillary degeneration occurs quite early. These changes consisted of a fibroblastic proliferation of the adventitia and hyperplasia of the lining endothelium Some of the vessels were converted to structureless hyalinized masses.

After cold injury,[57,102,103,104,105] an initial hyperemia is followed by capillary stasis with fluid loss from the capillaries and intracapillary

packing of the red cells. The capillary walls become rough and irregular and their course distorted. Blood flow continues in the a-v anastomoses and the thoroughfare channels. Edema begins with the onset of stasis, apparently because this type of flow favors an increased outward filtration. A brownish substance which has not been identified starts to accumulate outside the capillary. The injured part maintains a high temperature because of the continual blood flow through the a-v anastomosis and thoroughfare channels. This type of restricted flow also explains the low a-v oxygen difference of the injured part. Tissue that will become gangrenous develops a drop in temperature. Rapid thawing with heat delays the appearance of complete capillary stasis until it coincides in time with the period of maximal swelling and with reduced blood flow brought about by arterial constriction in the uninjured portion of the ear. Apparently sufficient circulation occurs to maintain conditions necessary for the survival of tissue not initially killed by the cold injury. Stellate ganglion block also delays the appearance of stasis in the capillaries of the rabbit ears studied, but the tissue still goes on to gangrene. Padded casts and pressure dressings, especially when used with rapid thawing, as well as the use of heparin apparently help maintain the nutrition of the cells in cold-injured tissue and also tend to prevent the development of gangrene. In frost bite,[103,106] "permeability" increases, but after the initial phase the capillaries are apparently normal. Sludge formation followed by the thrombus formation has been noted by some observers in frost bite.

In burns,[107,108] as in cold injury, increased capillary "permeability" occurs followed by capillary stasis which varies in time of occurrence with the severity of the burn. ACTH and cortisone[109] do not affect the development of edema in the period immediately following the burns.

Patients with glaucoma[110] have normal capillary fragility and a normal appearance of the nail bed capillaries. After histamine injections, they have less of an increase in skin capillary counts than normal patients. Capillary filtration as estimated by cutaneous lymph flow tends to be increased in those patients that have glaucoma, especially if they have glaucomatous disks.

In patients with allergic disease other than allergic purpura, the consensus is that there is no increase in capillary fragility or permeability.[68,111]

Capillary studies in other diseases have been made, but the results are not conclusive. In arthritis and in osteoarthropathy, the reports implicating skin capillaries are contradictory. In thromboangiitis obliterans, the skin capillary circulation is apparently not characteristic, and it would seem to be dependent at least in part on the pathology in the other vessels.

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